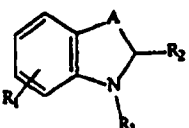
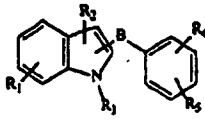
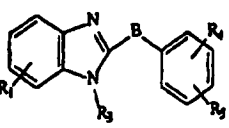
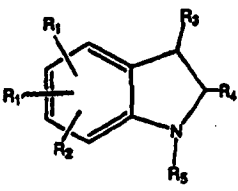
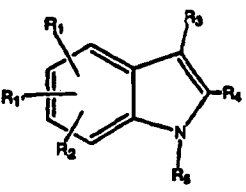
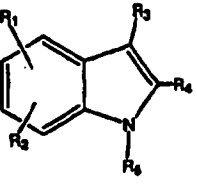




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<p>(51) International Patent Classification <sup>6</sup> : C07D 417/06, A61K 31/40, C07D 409/04, 401/12, 403/04, 209/22, 209/12, 209/10, 401/06, 209/42, 209/14, 403/06, 405/04, 417/10, 405/12</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 99/43672</b> (43) International Publication Date: 2 September 1999 (02.09.99)</p>
<p>(21) International Application Number: PCT/US99/03388 (22) International Filing Date: 17 February 1999 (17.02.99) (30) Priority Data: 09/030,102 25 February 1998 (25.02.98) US (71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US). (72) Inventors: SEEHRA, Jasbir, S.; 6211 Lexington Ridge, Lexington, MA 02173 (US). XIANG, YiBin; 821 Main Street, Acton, MA 01720 (US). BEMIS, Jean; 256 Appleton Street, Arlington, MA 02174 (US). McKEW, John; 58 Varnum Street, Arlington, MA 02174 (US). KAILA, Neelu; 2 Course Brook Lane, Natick, MA 01760 (US). CHEN, Lihren; 21 Madison Avenue, Cambridge, MA 02140 (US). (74) Agent: BROWN, Scott, A.; American Home Products Corporation, Patent and Trademark Dept. - 2B, One Campus Drive - attn. Kay E. Brady, Parsippany, NJ 07054 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: INHIBITORS OF PHOSPHOLIPASE A2</p> <div style="display: flex; flex-wrap: wrap; justify-content: space-around;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(II)</p> </div> <div style="text-align: center;">  <p>(III)</p> </div> <div style="text-align: center;">  <p>(IV)</p> </div> <div style="text-align: center;">  <p>(V)</p> </div> <div style="text-align: center;">  <p>(VI)</p> </div> </div> <p>(57) Abstract</p> <p>Inhibitors of cPLA<sub>2</sub> activity are disclosed, having a chemical formula selected from the group consisting of (I), (II), and (III), (IV), (V) or (VI).</p>		

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## INHIBITORS OF PHOSPHOLIPASE A2

This application is a continuation-in-part of application Ser. No. 08/918,400, filed August 26, 1997, which was a continuation of application Ser. No. 08/703,115, August 26, 1996.

Background of the Invention

The present invention relates to chemical inhibitors of the activity of various phospholipase enzymes, particularly phospholipase A<sub>2</sub> enzymes.

Leukotrienes and prostaglandins are important mediators of inflammation. Leukotrienes recruit inflammatory cells such as neutrophils to an inflamed site, promote the extravasation of these cells and stimulate release of superoxide and proteases which damage the tissue. Leukotrienes also play a pathophysiological role in the hypersensitivity experienced by asthmatics [See, e.g. B. Samuelson et al., *Science*, 237:1171-76 (1987)]. Prostaglandins enhance inflammation by increasing blood flow and therefore infiltration of leukocytes to inflamed sites. Prostaglandins also potentiate the pain response induced by stimuli.

Prostaglandins and leukotrienes are unstable and are not stored in cells, but are instead synthesized [W. L. Smith, *Biochem. J.*, 259:315-324 (1989)] from arachidonic acid in response to stimuli. Prostaglandins are produced from arachidonic acid by the action of COX-1 and COX-2 enzymes. Arachidonic acid is also the substrate for the distinct enzyme pathway leading to the production of leukotrienes.

Arachidonic acid which is fed into these two distinct inflammatory pathways is released from the sn-2 position of membrane phospholipids by phospholipase A<sub>2</sub> (hereinafter PLA<sub>2</sub>). The reaction catalyzed by PLA<sub>2</sub> is believed to represent the rate-limiting step in the process of lipid mediated biosynthesis and the production of inflammatory prostaglandins and leukotrienes. When the phospholipid substrate of PLA<sub>2</sub> is of the phosphatidyl choline class with an ether linkage in the sn-1 position, the lysophospholipid produced is the immediate precursor of platelet activating factor (hereafter called PAF), another potent mediator of inflammation [S.I. Wasserman, *Hospital Practice*, 15:49-58 (1988)].

Most anti-inflammatory therapies have focussed on preventing production of either prostaglandins or leukotrienes from these distinct pathways, but not on all of them. For example, ibuprofen, aspirin and indomethacin are all NSAIDs which inhibit the production of prostaglandins by

COX-1/COX-2, but have no effect on the inflammatory production of leukotrienes from arachidonic acid in the other pathways. Conversely, zileuton inhibits only the pathway of conversion of arachidonic acid to leukotrienes, without affecting the production of prostaglandins. None of these widely-used anti-inflammatory agents affects the production of PAF.

Consequently the direct inhibition of the activity of  $PLA_2$  has been suggested as a useful mechanism for a therapeutic agent, i.e., to interfere with the inflammatory response. [See, e.g., J. Chang et al, Biochem. Pharmacol., **36**:2429-2436 (1987)].

A family of  $PLA_2$  enzymes characterized by the presence of a secretion signal sequenced and ultimately secreted from the cell have been sequenced and structurally defined. These secreted  $PLA_2$ s have an approximately 14 kD molecular weight and contain seven disulfide bonds which are necessary for activity. These  $PLA_2$ s are found in large quantities in mammalian pancreas, bee venom, and various snake venom. [See, e.g., references 13-15 in Chang et al, cited above; and E. A. Dennis, Drug Devel. Res., **10**:205-220 (1987).] However, the pancreatic enzyme is believed to serve a digestive function and, as such, should not be important in the production of the inflammatory mediators whose production must be tightly regulated.

The primary structure of the first human non-pancreatic  $PLA_2$  has been determined. This non-pancreatic  $PLA_2$  is found in platelets, synovial fluid, and spleen and is also a secreted enzyme. This enzyme is a member of the aforementioned family. [See, J. J. Seilhamer et al, J. Biol. Chem., **264**:5335-5338 (1989); R. M. Kramer et al, J. Biol. Chem., **264**:5768-5775 (1989); and A. Kando et al, Biochem. Biophys. Res. Comm., **163**:42-48 (1989)]. However, it is doubtful that this enzyme is important in the synthesis of prostaglandins, leukotrienes and PAF, since the non-pancreatic  $PLA_2$  is an extracellular protein which would be difficult to regulate, and the next enzymes in the biosynthetic pathways for these compounds are intracellular proteins. Moreover, there is evidence that  $PLA_2$  is regulated by protein kinase C and G proteins [R. Burch and J. Axelrod, Proc. Natl. Acad. Sci. U.S.A., **84**:6374-6378 (1989)] which are cytosolic proteins which must act on intracellular proteins. It would be impossible for the non-pancreatic  $PLA_2$  to function in the cytosol, since the high reduction potential would reduce the disulfide bonds and inactivate the enzyme.

A murine  $PLA_2$  has been identified in the murine macrophage cell line, designated RAW 264.7. A specific activity of 2  $\mu$ mol/min/mg, resistant to reducing conditions, was reported to be associated with the approximately 60 kD molecule. However, this protein was not purified to homogeneity. [See, C. C. Leslie et al, Biochem. Biophys. Acta., **963**:476-492 (1988)]. The references cited above are incorporated by reference herein for information pertaining to the function of the phospholipase



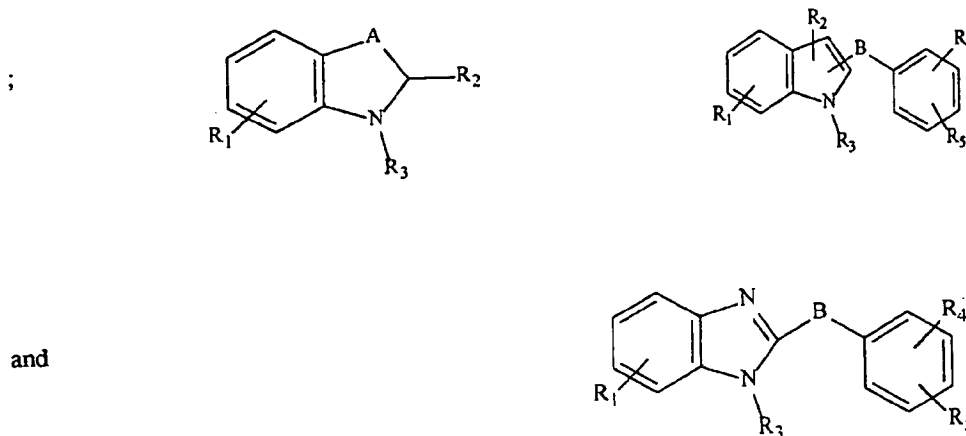
enzymes, particularly PLA<sub>2</sub>.

A cytosolic phospholipase A<sub>2</sub> (hereinafter "cPLA<sub>2</sub>") has also been identified and cloned. See, U.S. Patent Nos. 5,322,776 and 5,354,677, which are incorporated herein by reference as if fully set forth. The enzyme of these patents is an intracellular PLA<sub>2</sub> enzyme, purified from its natural source or otherwise produced in purified form, which functions intracellularly to produce arachidonic acid in response to inflammatory stimuli.

Now that several phospholipase enzymes have been identified, it would be desirable to identify chemical inhibitors of the action of enzymes, which inhibitors could be used to treat inflammatory conditions, particularly where inhibition of production of prostaglandins, leukotrienes and PAF are all desired. There remains a need in the art for an identification of such anti-inflammatory agents for therapeutic use in a variety of disease states.

Summary of the Invention

The present invention provides compounds having a chemical formula selected from the group consisting of:



or a pharmaceutically acceptable salt thereof, wherein:

A is independent of any other group and is selected from the group consisting of  $-\text{CH}_2-$  and  $-\text{CH}_2\text{-CH}_2-$ ;

B is independent of any other group and is selected from the group consisting of  $-(\text{CH}_2)_n-$ ,  $-(\text{CH}_2\text{O})_n-$ ,  $-(\text{CH}_2\text{S})_n-$ ,  $-(\text{OCH}_2)_n-$ ,  $-(\text{SCH}_2)_n-$ ,  $-(\text{CH}=\text{CH})_n-$ ,  $-(\text{C}\equiv\text{C})_n-$ ,  $-\text{CON}(\text{R}_6)-$ ,  $-\text{N}(\text{R}_6)\text{CO}-$ ,  $-\text{O}-$ ,  $-\text{S}-$  and  $-\text{N}(\text{R}_6)-$ ;

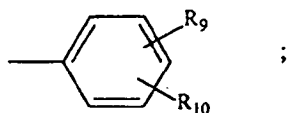
$\text{R}_1$  is independent of any other R group and is selected from the group consisting of  $-\text{X}-\text{R}$ ,  $-\text{H}$ ,  $-\text{OH}$ , halogen,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $\text{C}_1$ - $\text{C}_5$  alkyl, alkenyl, alkynyl, aryl and substituted aryl;

$\text{R}_2$  is independent of any other R group and is selected from the group consisting of  $-\text{H}$ ,  $-\text{COOH}$ ,  $-\text{COR}_5$ ,  $-\text{CONR}_5\text{R}_6$ ,  $-(\text{CH}_2)_n\text{-W-(CH}_2)_m\text{-Z-R}_5$ ,  $-(\text{CH}_2)_n\text{-W-R}_5$ ,  $-\text{Z-R}_5$ ,  $\text{C}_1$ - $\text{C}_{10}$  alkyl, alkenyl and substituted aryl;

$\text{R}_3$  is independent of any other R group and is selected from the group consisting of  $-\text{H}$ ,  $-\text{COOH}$ ,  $-\text{COR}_5$ ,  $-\text{CONR}_5\text{R}_6$ ,  $-(\text{CH}_2)_n\text{-W-(CH}_2)_m\text{-Z-R}_5$ ,  $-(\text{CH}_2)_n\text{-W-R}_5$ ,  $-\text{Z-R}_5$ ,  $\text{C}_1$ - $\text{C}_{10}$  alkyl, alkenyl and substituted aryl;

$\text{R}_4$  is independent of any other R group and is selected from the group consisting of  $-\text{H}$ ,  $-\text{OH}$ ,  $-\text{OR}_6$ ,  $-\text{SR}_6$ ,  $-\text{CN}$ ,  $-\text{COR}_6$ ,  $-\text{NHR}_6$ ,  $-\text{COOH}$ ,  $-\text{CONR}_6\text{R}_7$ ,  $-\text{NO}_2$ ,  $-\text{CONHSO}_2\text{R}_8$ ,  $\text{C}_1$ - $\text{C}_5$  alkyl, alkenyl and substituted aryl;

$R_5$  is independent of any other R group and is selected from the group consisting of -H, -OH, - $O(CH_2)_nR_6$ , - $SR_6$ , -CN, - $COR_6$ , - $NHR_6$ , -COOH, - $NO_2$ , -COOH, - $CONR_6R_7$ , - $CONHSO_2R_8$ ,  $C_1-C_5$  alkyl, alkenyl, alkynyl, aryl, substituted aryl, - $CF_3$ , - $CF_2CF_3$  and



$R_6$  is independent of any other R group and is selected from the group consisting of -H,  $\text{C}_1-C_5$  alkyl, alkenyl, alkynyl, aryl and substituted aryl;

$R_7$  is independent of any other R group and is selected from the group consisting of -H,  $\text{C}_1-C_5$  alkyl, alkenyl, alkynyl, aryl and substituted aryl;

$R_8$  is independent of any other R group and is selected from the group consisting of  $\text{C}_1-C_5$  alkyl, aryl and substituted aryl;

$R_9$  is independent of any other R group and is selected from the group consisting of -H, -OH, a halogen, -CN, - $OR_6$ , -COOH, - $CONR_6R_7$ , tetrazole, - $CONHSO_2R_8$ , - $COR_6$ , - $(CH_2)_nCH(OH)R_6$  and - $(CH_2)_nCH(R_6)R_5$ ;

$R_{10}$  is independent of any other R group and is selected from the group consisting of -H, -OH, a halogen, -CN, - $OR_6$ , -COOH, - $CONR_6R_7$ , tetrazole, - $CONHSO_2R_8$ , - $COR_6$ , - $(CH_2)_nCH(OH)R_6$  and - $(CH_2)_nCH(R_6)R_5$ ;

W is, independently each time used including within the same compound, selected from the group consisting of -O-, -S-, - $CH_2$ -, - $CH=CH$ -, - $C \equiv C$ - and - $N(R_6)$ -;

X is independent of any other group and is, independently each time used including within the same compound, selected from the group consisting of -O-, -S- and - $N(R_6)$ -;

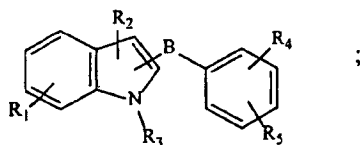
Z is independent of any other group and is, independently each time used including within the same compound, selected from the group consisting of - $CH_2$ -, -O-, -S-, - $N(R_6)$ -, -CO-, - $CON(R_6)$ - and - $N(R_6)CO$ -;

m is, independently each time used including within the same compound, an integer from 0 to 4; and

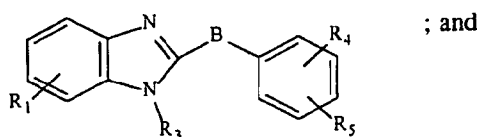
n is independent of m and is, independently each time used including within the same compound, an integer from 0 to 4.

Preferably, the compounds of the invention have phospholipase enzyme inhibiting activity. Other

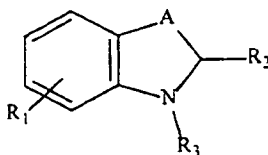
preferred embodiments include compounds having the following chemical formula:



compounds having the following chemical formula:



; and

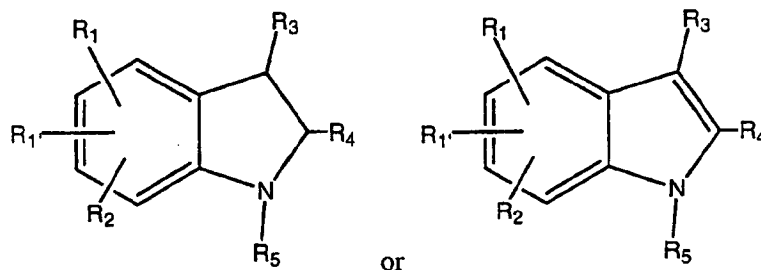


compounds having the following  
chemical formula:

In particularly preferred embodiments, A is  $-\text{CH}_2-$  and  $\text{R}_2$  is  $-(\text{CH}_2)_n-\text{W}-(\text{CH}_2)_m-\text{ZR}_5$ . These preferred compounds includes those wherein n is 1, m is 1, W is  $-\text{S}-$  and Z is  $-\text{CO}-$ ; those wherein  $\text{R}_5$  is  $-\text{NHR}_6$ ; those wherein  $\text{R}_6$  is a substituted aryl group and those wherein said aryl group is substituted with one or more substituents independently selected from the group consisting of a halogen,  $-\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_3$ ,  $-(\text{CH}_2)_p\text{COOH}$ ,  $-(\text{CH}_2)_p\text{CH}_3$ ,  $-\text{O}(\text{CH}_2)_p\text{CH}_3$ ,  $-(\text{CH}_2)_p\text{OH}$ ,  $-(\text{CH}_2)_p\text{S}(\text{C}_6\text{H}_5)$ ,  $-(\text{CH}_2)_p\text{CONH}_2$  and  $-\text{CHR}_{11}\text{COOH}$ , wherein  $\text{R}_{11}$  is selected from the group consisting of alkyl, alkenyl, alkynyl,  $-(\text{CH}_2)_p\text{OH}$ , and  $-\text{O}(\text{CH}_2)_p\text{CH}_3$ , and wherein p is an integer from 0 to 4. Other preferred compounds include those wherein  $\text{R}_1$  is selected from the group consisting of  $-\text{H}$  and  $-\text{OCH}_2(\text{C}_6\text{H}_5)$  and  $\text{R}_3$

is  $-\text{COR}_5$ ,  $\text{R}_5$  is  $-\text{OCH}_2\text{R}_6$  and  $\text{R}_6$  is a substituted aryl group. In particularly preferred compounds, said aryl group is substituted with one or more substituents selected from the group consisting of  $-\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_3$  and  $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$ .

Among the compounds of this invention are those of the formula:



wherein :

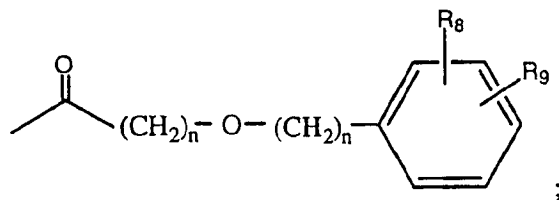
$R_1$  and  $R_{1'}$  are independently selected from  $C_1$ - $C_6$  alkyl,  $-Z$ - $C_1$ - $C_6$  alkyl, phenyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -phenyl, benzyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -benzyl, naphthyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -naphthyl, pyrimidinyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -pyrimidinyl, the alkyl, phenyl, benzyl, naphthyl and pyrimidinyl groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ , or  $-OH$ ;

$Z$  is O or S;

$n$  is an integer from 0 to 3;

$R_2$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH$ - $C_1$ - $C_6$  alkyl,  $-N(C_1$ - $C_6$  alkyl) $_2$ ,  $-N$ - $SO_2$ - $C_1$ - $C_6$  alkyl, or  $-SO_2$ - $C_1$ - $C_6$  alkyl;

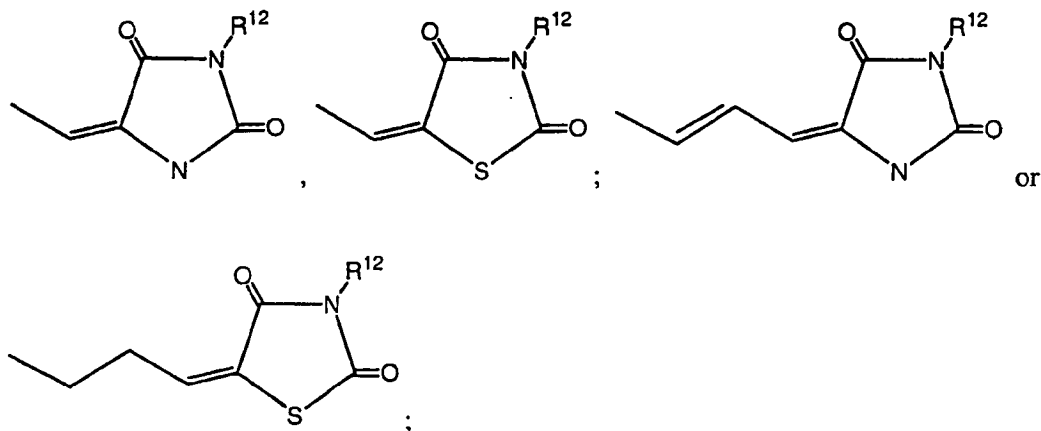
$R_3$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy,  $-CHO$ ,  $-C(O)CH_3$ ,  $-C(O)$ -( $CH_2$ ) $_n$ - $CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH$ - $C_1$ - $C_6$  alkyl,  $-N(C_1$ - $C_6$  alkyl) $_2$ ,  $-N$ - $SO_2$ - $C_1$ - $C_6$  alkyl,  $-SO_2$ - $C_1$ - $C_6$  alkyl or a moiety of the formula:



$n$  in each appearance is independently selected as an integer selected from 0-3;

$R^8$  and  $R^9$  are independently selected in each appearance from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,  $-\text{NH}(\text{C}_1-\text{C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})_2$ ;

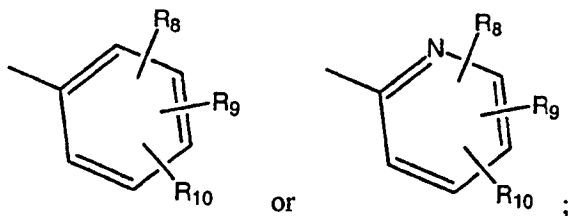
$R_4$  is selected from  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{CH}=\text{CH}-\text{COOH}$ , tetrazole,  $-(\text{CH}_2)_n$ -tetrazole, the moiety  $-\text{L}^1-\text{M}^1$  or a moiety of the formulae:



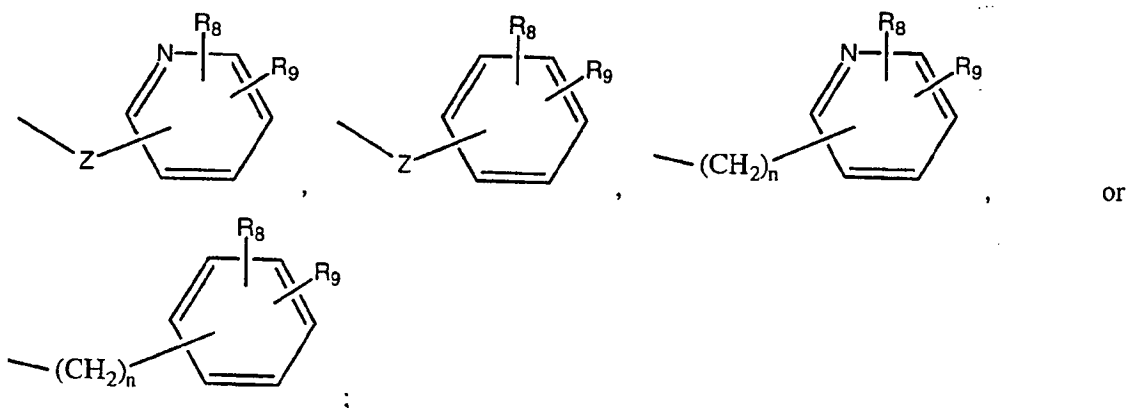
$R^{12}$  is selected from H,  $-\text{CF}_3$ ,  $\text{C}_1-\text{C}_6$  alkyl,  $-(\text{CH}_2)_n-\text{C}_3-\text{C}_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,  $-\text{NH}(\text{C}_1-\text{C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})_2$ ;

$\text{L}^1$  is selected from  $-(\text{CH}_2)_n-\text{O}-$ ,  $-(\text{CH}_2)_n-\text{S}-$ ,  $-(\text{CH}_2)_n-\text{O}-(\text{CH}_2)_n-$ ,  $-(\text{CH}_2)_n-\text{S}-(\text{CH}_2)_n-$ ,  $-\text{C(O)}-\text{O}-$ ,  $-\text{C(O)}-(\text{CH}_2)_n-\text{O}-$ ,  $-\text{C(O)}-\text{N}-$ , or  $-(\text{CH}_2)_n-\text{S}-(\text{CH}_2)_n-\text{C(O)}-\text{N}-$ ;

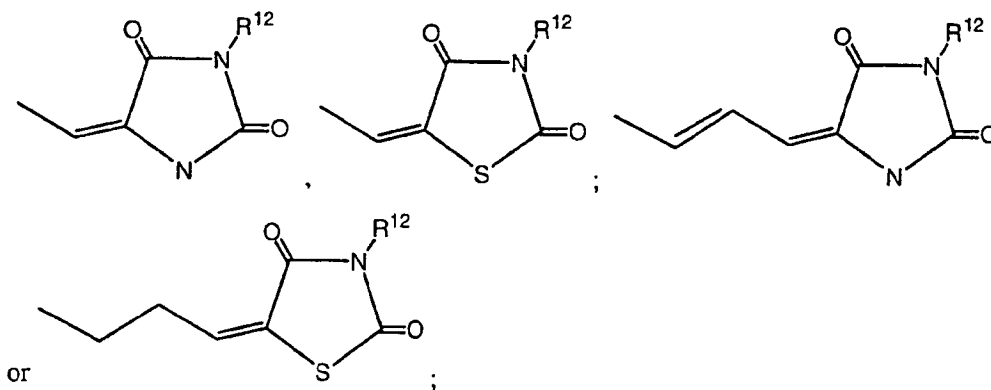
$\text{M}^1$  is  $-\text{COOH}$  or a moiety selected from:



$R^{10}$  is selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,



with a proviso that the moiety or combination of moieties comprising  $R^3$  include an acidic group selected from carboxylic acid or a moiety of the formulae:



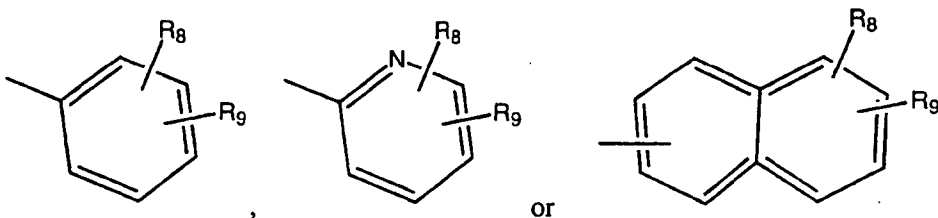


$R_5$  is selected from:

a) a moiety of the formula  $-L^2-M^2$ ;

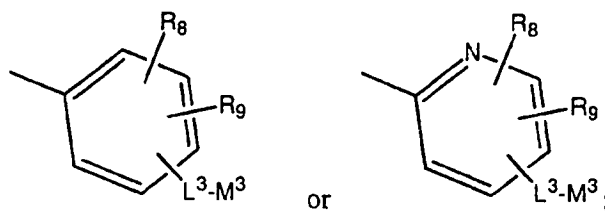
$L^2$  is selected from a chemical bond or a bridging group selected from  $-(CH_2)_n-Z-$ ,  $-(CH_2)_n-Z-(CH_2)_n-$ ,  $-C(O)-O-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

$M^2$  is selected from  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,



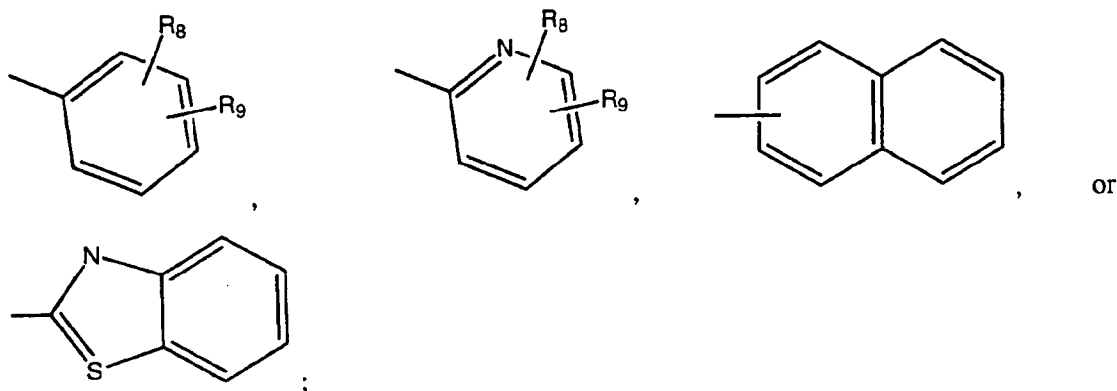
wherein  $R^8$  and  $R^9$  are as defined above and can be substituted anywhere on the cyclic or bicyclic ring; or

b) a moiety of the formulae:



wherein  $L^3$  is a chemical bond or a group selected from  $-CH_2-$ ,  $-CH_2-Z-$ ,  $-C(O)-$ ,  $-O-$ ,  $-S-$ , or  $-(CH_2)_n-Z-(CH_2)_n-$ ;

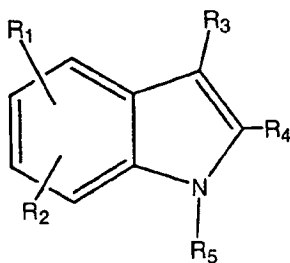
$M^3$  is selected from  $-(CH_2)_n-C_3-C_5$  cycloalkyl, furanyl, thienyl, pyrrolyl,



or a pharmaceutically acceptable salt thereof.

Of the compounds in the group just defined, a preferred subset include those in which the core molecule is an indole. Within the indole group is another subset wherein  $R^1$  and  $R^2$  are hydrogen, and the moieties  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^8$ ,  $R^9$  and  $R^{10}$ ,  $n$ ,  $L^1$ ,  $L^2$ ,  $M^1$  and  $M^2$  are as defined above. Within this subset is another preferred group wherein  $R^1$  is in the indole 5-position.

Also among the compounds of this invention are those of the formula:

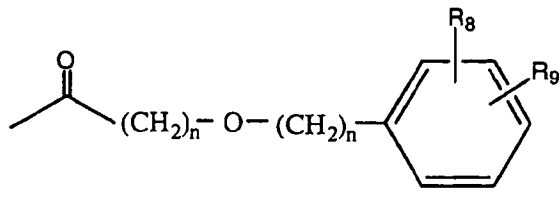


wherein :

$R_1$  is selected from -O- $C_1$ - $C_6$  alkyl, -S- $C_1$ - $C_6$  alkyl, -O-phenyl, -S-phenyl, -O-benzyl, -S-benzyl, the alkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub>, or -OH;

$R_2$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl, preferably  $-C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH-C_1-C_6$  alkyl,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-N-SO_2-C_1-C_6$  alkyl, or  $-SO_2-C_1-C_6$  alkyl;

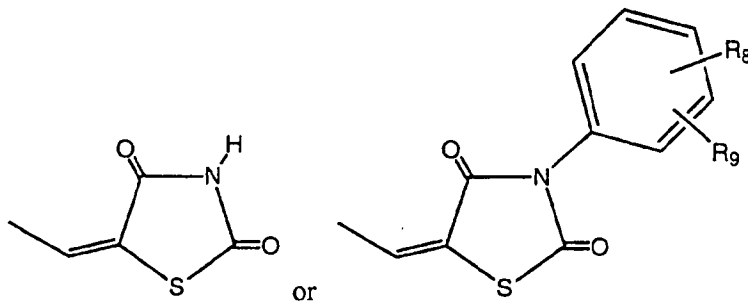
$R_3$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl, preferably  $-C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH-C_1-C_6$  alkyl,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-N-SO_2-C_1-C_6$  alkyl,  $-SO_2-C_1-C_6$  alkyl, or a moiety of the formula:



$n$  in each appearance is independently selected as an integer selected from 0-3;

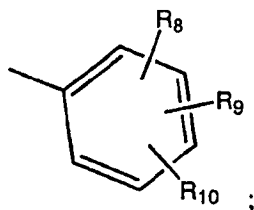
$R^8$  and  $R^9$  are independently selected in each appearance from H,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-CF_3$ ,  $-OH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,  $-NH(C_1-C_6 \text{ alkyl})$ , or  $-N(C_1-C_6 \text{ alkyl})_2$ ;

$R_4$  is the moiety  $-L^1-M^1$  or

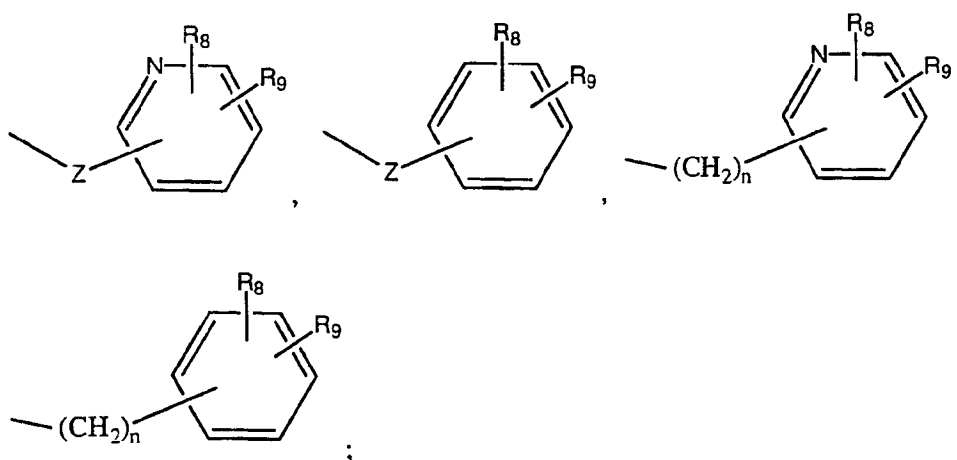


$L^1$  is selected from a chemical bond or a bridging group selected from  $-(CH_2)_n-O-$ ,  $-(CH_2)_n-S-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-C(O)-O-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

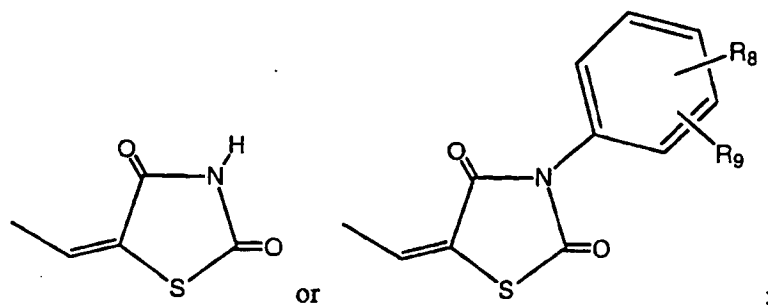
M<sup>1</sup> is the moiety:



R<sup>10</sup> is selected from H, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CF<sub>3</sub>, -OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -C<sub>1</sub>-C<sub>6</sub> alkyl, -O-C<sub>1</sub>-C<sub>6</sub> alkyl,



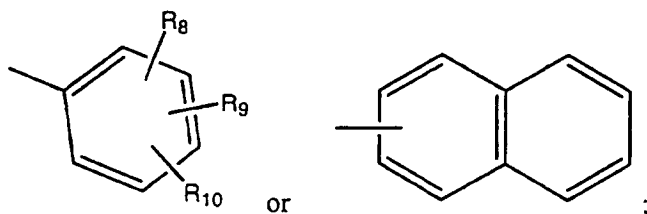
with a proviso that the combination of moieties comprising R<sup>4</sup> include a carboxylic acid or a moiety of the formulae:



$R_5$  is a structure of the formula  $-L^2-M^2$ ;

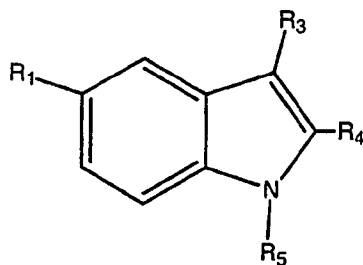
$L^2$  is selected from a chemical bond or a bridging group selected from  $-(CH_2)_n-O-$ ,  $-(CH_2)_n-S-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-C(O)-O-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

$M^2$  is selected from  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,



wherein  $R^8$ ,  $R^9$  and  $R^{10}$  are as defined above;  
or a pharmaceutically acceptable salt thereof.

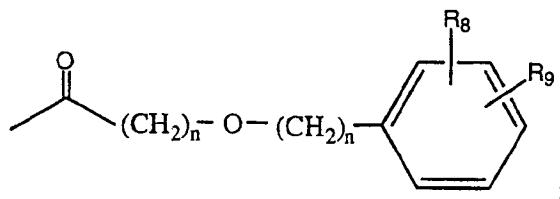
Also preferred are compounds of the group above with the structure:



wherein

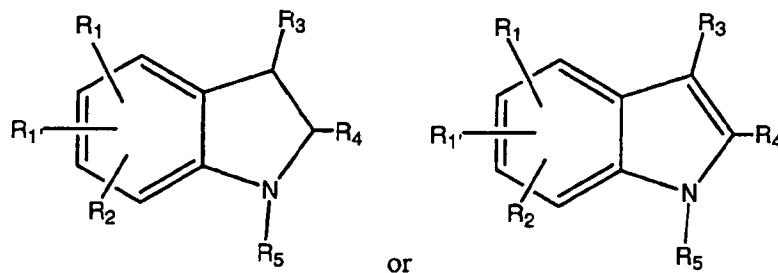
$R_1$  is selected from  $-O-C_1-C_6$  alkyl,  $-S-C_1-C_6$  alkyl,  $-O$ -phenyl,  $-O$ -benzyl,  $-S$ -benzyl, the alkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ , or  $-OH$ ;

$R_3$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl, preferably  $-C_1-C_{10}$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_{10}$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH-C_1-C_6$  alkyl,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-N-SO_2-C_1-C_6$  alkyl,  $-SO_2-C_1-C_6$  alkyl or a moiety of the formula:



wherein  $R^4$ ,  $R^5$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  are as defined above, or a pharmaceutically acceptable salt thereof.

Also among the compounds of the present invention are those of the formulae:



wherein

$R_1$  and  $R_2$  are independently selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl, preferably  $-C_1-C_6$  alkyl,  $-S-C_1-C_{10}$  alkyl, preferably  $-S-C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ , phenyl,  $-O$ -phenyl,  $-S$ -phenyl, benzyl,  $-O$ -benzyl,  $-S$ -benzyl; or a ring moiety of the groups a), b) or c), below, directly bonded to the indole ring or bonded to the indole ring by a  $-S-$ ,  $-O-$  or  $-(CH_2)_n-$  bridge;

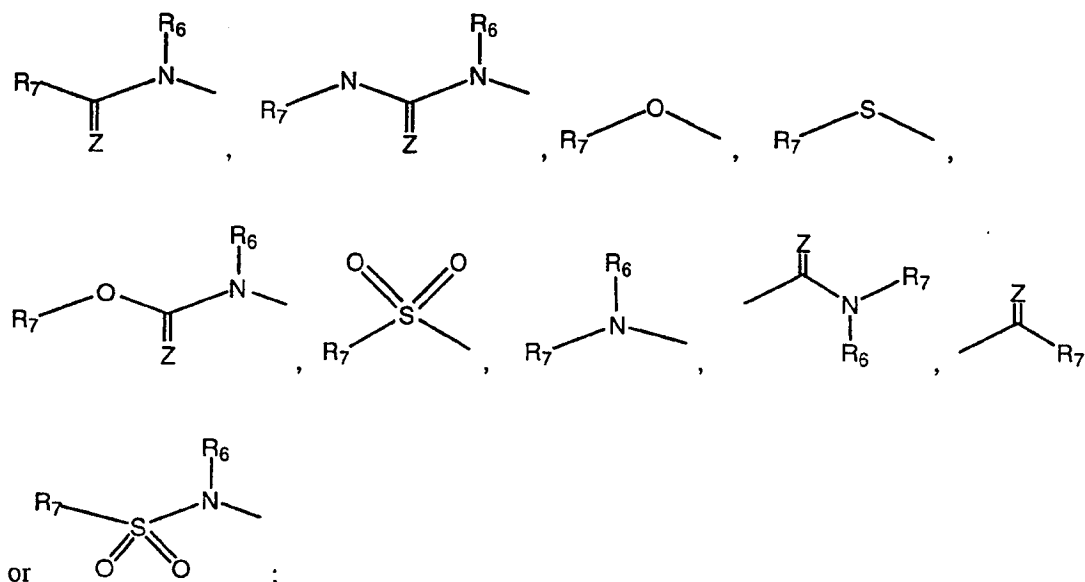
a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, oxathiazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ ; or

b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadiazine, oxazine, or morpholine, the six-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ; or

c) a bicyclic ring moiety optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to, benzofuran, chromene, indole, isoindole, indoline, isoindoline, naphthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine,

quinazoline, cinnoline, phthalazine, or naphthyridine, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

d) a moiety of the formulae:



Z is O or S;

R<sub>6</sub> is selected from the relevant members of the group H, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-benzyl, or -S-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub>, or -OH;

R<sub>7</sub> is selected from the relevant members of the group -OH, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub>, -NH-(C<sub>1</sub>-C<sub>6</sub> alkyl), -



$N-(C_1-C_6 \text{ alkyl})_2$ ,  $-(CH_2)_n-NH-(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_n-N-(C_1-C_6 \text{ alkyl})_2$ , phenyl, -O-phenyl, benzyl, or -O-benzyl; or

a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, oxathiazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ , or  $-CF_3$ ; or

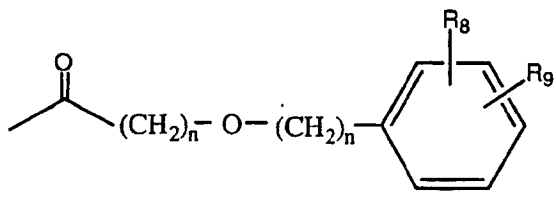
b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadiazine, oxazine, or morpholine, the six-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ; or

c) a bicyclic ring moiety containing from 8 to 10 ring atoms and optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to, benzofuran, chromene, indole, isoindole, indoline, isoindoline, naphthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine, quinazoline, cinnoline, phthalazine, or naphthyridine, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ;

n is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2;

$R_2$  is selected from H, halogen,  $-CN$ ,  $-CHO$ ,  $-CF_3$ ,  $-OH$ ,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH-C_1-C_6$  alkyl,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-N-SO_2-C_1-C_6$  alkyl, or  $-SO_2-C_1-C_6$  alkyl;

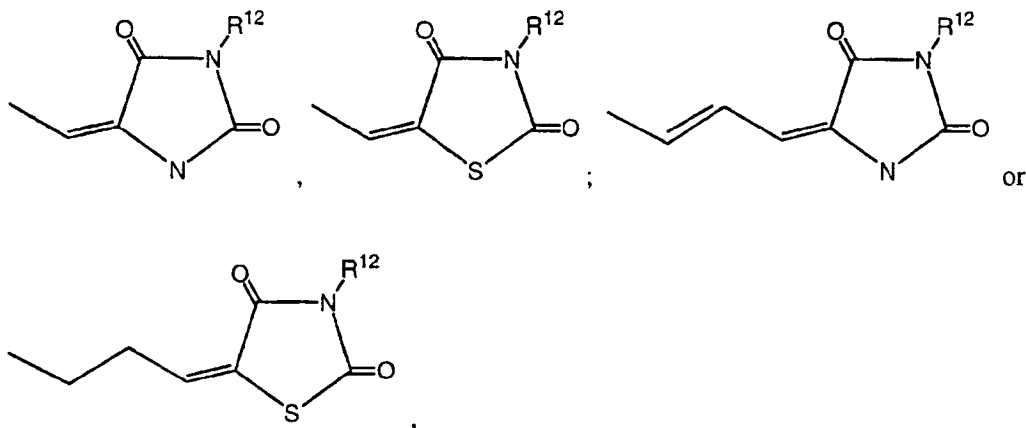
$R_3$  is selected from H, halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_1\text{-C}_{10}$  alkoxy,  $-\text{CHO}$ ,  $-\text{C}(\text{O})\text{CH}_3$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_n\text{-CF}_3$ ,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{NH}_2$ ,  $-\text{NH-C}_1\text{-C}_6$  alkyl,  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ ,  $-\text{N-SO}_2\text{-C}_1\text{-C}_6$  alkyl,  $-\text{SO}_2\text{-C}_1\text{-C}_6$  alkyl, phenyl, phenyloxy, benzyl, benzyloxy- $\text{C}(\text{O})$ -phenyl,  $-\text{C}(\text{O})$ -benzyl,  $-\text{CH}_2\text{-(C}_3\text{-C}_6 \text{ cycloalkyl)}$ ,  $-\text{C}(\text{O})\text{-OH}$ ,  $\text{C}(\text{O})\text{-C}_1\text{-C}_6$  alkyl,  $-\text{C}(\text{O})\text{-O-C}_1\text{-C}_6$  alkyl,  $-\text{C}(\text{O})\text{-CF}_3$ ,  $-(\text{CH}_2)_n\text{-S-CH}_2\text{-(C}_3\text{-C}_5 \text{ cycloalkyl)}$ , the rings of the relevant  $R_3$  groups being optionally substituted by from 1 to 3 groups selected from halogen,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{C}(\text{O})\text{-OH}$ , or  $-\text{OH}$ ; or a moiety of the formula:



$n$  in each appearance is an integer independently selected from 0-3;

$R^8$  and  $R^9$  are independently selected in each appearance from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C}(\text{O})\text{-COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n\text{-C}(\text{O})\text{-COOH}$ ,  $-\text{C}_1\text{-C}_6$  alkyl,  $-\text{O-C}_1\text{-C}_6$  alkyl,  $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ ;

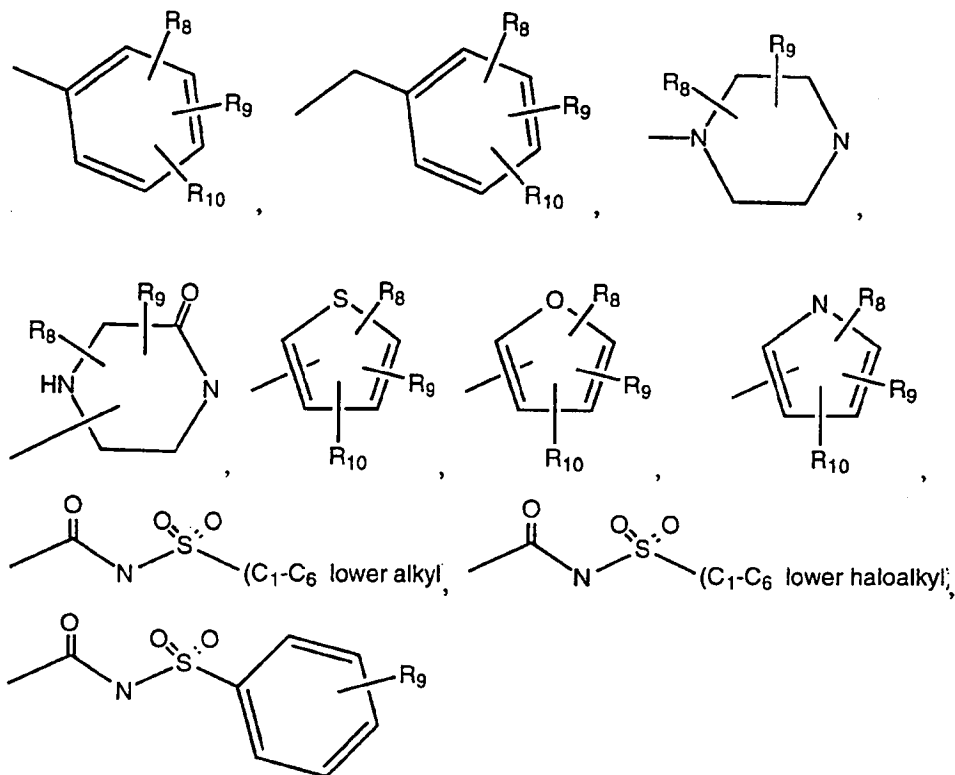
$R_4$  is selected from  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C}(\text{O})\text{-COOH}$ ,  $-\text{CH=CH-COOH}$ , tetrazole,  $-(\text{CH}_2)_n\text{-tetrazole}$ , the moiety  $-\text{L}^1\text{-M}^1$  or a moiety of the formulae:

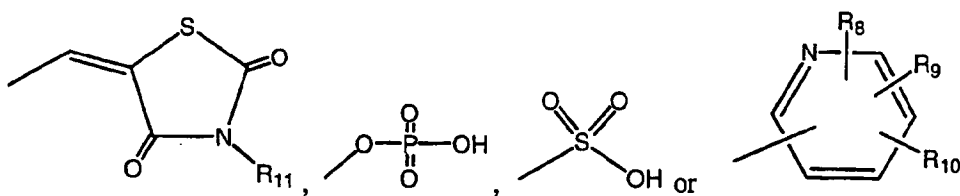


$R^{12}$  is selected from H,  $-CF_3$ ,  $C_1-C_6$  alkyl,  $-(CH_2)_n-C_3-C_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-CF_3$ ,  $-OH$ ,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,  $-NH(C_1-C_6$  alkyl), or  $-N(C_1-C_6$  alkyl) $_2$ ;

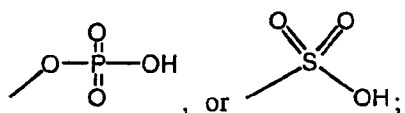
$L^1$  is selected from  $-(CH_2)_n-$ ,  $-S-$ ,  $-O-$ ,  $-C(O)-$ ,  $-C(O)-O-$ ,  $-(CH_2)_n-O-$ ,  $-(CH_2)_n-S-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-(CH_2)_n-C(O)-(CH_2)_n-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-C(Z)-N(R_6)-$ ,  $-C(Z)-N(R_6)-(CH_2)_n-$ ,  $-C(O)-C(Z)-N(R_6)-$ ,  $-C(O)-C(Z)-N(R_6)-(CH_2)_n-$ ,  $-C(Z)-NH-SO_2-$ ,  $-C(Z)-NH-SO_2-(CH_2)_n-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

$M^1$  is  $-COOH$  or a moiety selected from:





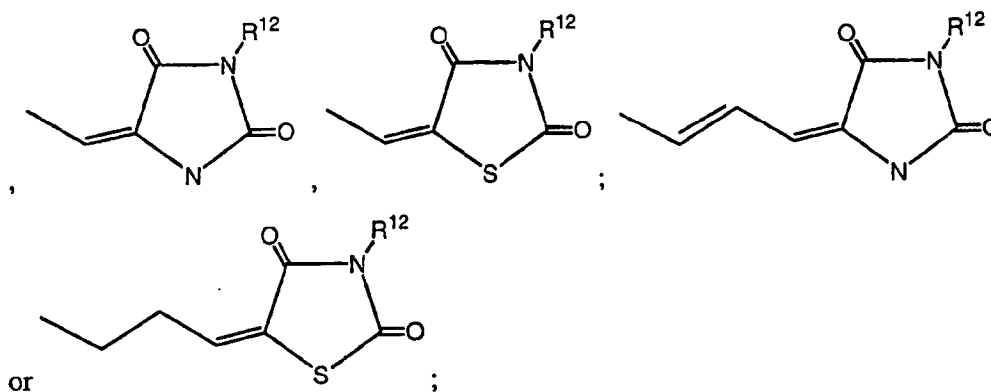
$R_8$ , in each appearance, is independently selected from H,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ , tetrazole,



$R_9$  in each appearance is independently selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,  $-NH(C_1-C_6$  alkyl), or  $-N(C_1-C_6$  alkyl) $_2$ ;

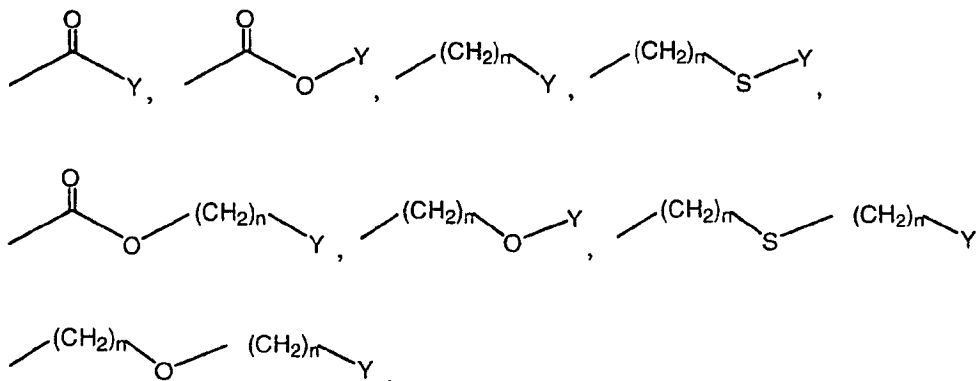
$R_{10}$  is selected from H,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-CF_3$ ,  $-OH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,





$R_5$  is selected from  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -S- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -O- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl, or the groups of:

a)  $-(CH_2)_n$ -phenyl-O-phenyl,  $-(CH_2)_n$ -phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -O-phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -phenyl-(O- $CH_2$ -phenyl) $_2$ ,  $-CH_2$ -phenyl-C(O)-benzothiazole or a moiety of the formulae:



wherein  $n$  is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2,

$Y$  is  $C_3$ - $C_5$  cycloalkyl or

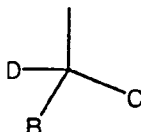
a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole,

isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, oxathiazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ , or  $-CF_3$ ; or

b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadiazine, oxazine, or morpholine, the six-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ; or

c) a bicyclic ring moiety containing from 8 to 10 ring atoms and optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to benzofuran, chromene, indole, isoindole, indoline, isoindoline, naphthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine, quinazoline, cinnoline, phthalazine, or naphthyridine, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ;

d) a moiety of the formulae  $-(CH_2)_n-A$ ,  $-(CH_2)_n-S-A$ , or  $-(CH_2)_n-O-A$ , wherein A is the moiety:



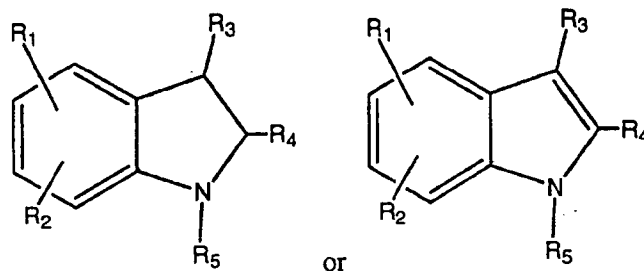
wherein

D is H,  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-CF_3$  or  $-(CH_2)_n-CF_3$ ;

B and C are independently selected from phenyl, pyridinyl, pyrimidinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen,  $-CN$ ,  $-CHO$ ,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-NH_2$  or  $-NO_2$ ;

or a pharmaceutically acceptable salt thereof.

Preferred compounds include those having the formula:



wherein

R<sub>1</sub> is selected from H, halogen, -CF<sub>3</sub>, -OH, -C<sub>1</sub>-C<sub>10</sub> alkyl, preferably -C<sub>1</sub>-C<sub>6</sub> alkyl, -S-C<sub>1</sub>-C<sub>10</sub> alkyl, preferably -S-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-benzyl, -S-benzyl; or a ring moiety of the groups a), b) or c), below, directly bonded to the indole ring or bonded to the indole ring by a -S-, -O- or - (CH<sub>2</sub>)<sub>n</sub>- bridge;

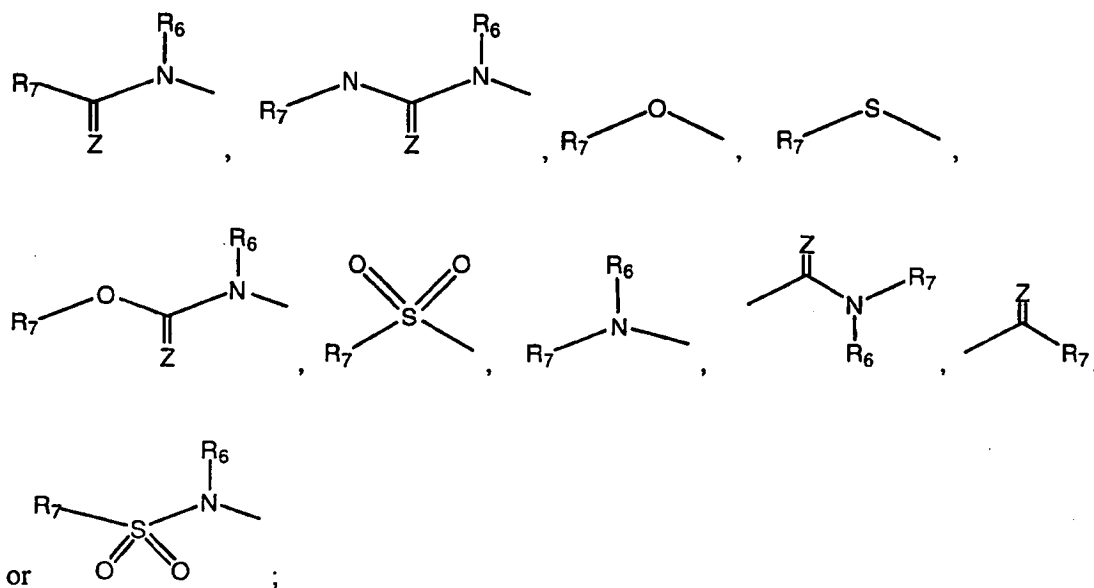
a) furan, pyrrole, or thiophene, being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub>; or

b) pyridine, pyrimidine, piperidine, or morpholine, each being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

c) benzofuran, indole, naphthalene, purine, or quinoline, each being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

d) a moiety of the formulae:





Z is O or S;

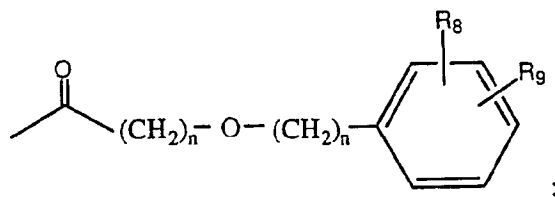
$R_6$  is selected from the relevant members of the group H,  $-CF_3$ ,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy, phenyl,  $-O$ -phenyl,  $-S$ -phenyl, benzyl,  $-O$ -benzyl, or  $-S$ -benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ , or  $-OH$ ;

$R_7$  is selected from the relevant members of the group  $-OH$ ,  $-CF_3$ ,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-NH_2$ ,  $-(CH_2)_n-NH_2$ ,  $-NH-(C_1-C_6 \text{ alkyl})$ ,  $-N-(C_1-C_6 \text{ alkyl})_2$ ,  $-(CH_2)_n-NH-(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_n-N-(C_1-C_6 \text{ alkyl})_2$ , phenyl,  $-O$ -phenyl, benzyl, or  $-O$ -benzyl, furan, pyrrole, thiophene, pyridine, pyrimidine, thiazole, pyrazole, or morpholine the rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ;

$n$  is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2;

$R_2$  is selected from H, halogen, -CN, -CHO, -CF<sub>3</sub>, -OH, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -N-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, or -SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl;

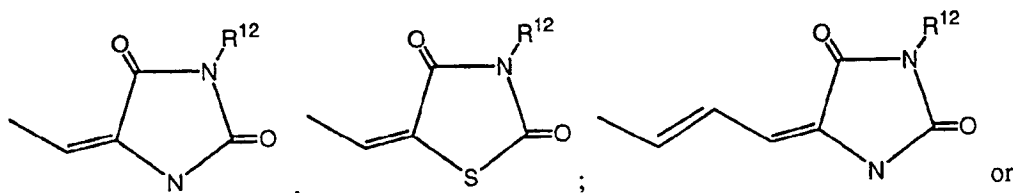
$R_3$  is selected from H, halogen, -CF<sub>3</sub>, -OH, -C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, -CHO, -C(O)CH<sub>3</sub>, -C(O)-(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -N-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, phenyloxy, benzyl, benzyloxy-C(O)-phenyl, -C(O)-benzyl, -CH<sub>2</sub>-(C<sub>3</sub>-C<sub>5</sub> cycloalkyl), -C(O)-OH, C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)-O-C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)-CF<sub>3</sub>, or -(CH<sub>2</sub>)<sub>n</sub>-S-CH<sub>2</sub>-(C<sub>3</sub>-C<sub>5</sub> cycloalkyl), the rings of the relevant  $R_3$  groups being optionally substituted by from 1 to 3 groups selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NO<sub>2</sub>, -CF<sub>3</sub>, -C(O)-OH, or -OH; or a moiety of the formula:

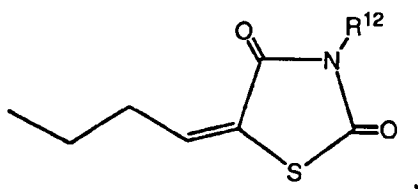


$n$  in each appearance is independently selected as an integer selected from 0-3;

$R^8$  and  $R^9$  are independently selected in each appearance from H, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CF<sub>3</sub>, -OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -C<sub>1</sub>-C<sub>6</sub> alkyl, -O-C<sub>1</sub>-C<sub>6</sub> alkyl, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>;

$R_4$  is selected from -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CH=CH-COOH, tetrazole, -(CH<sub>2</sub>)<sub>n</sub>-tetrazole, the moiety -L<sup>1</sup>-M<sup>1</sup> or a moiety of the formulae:

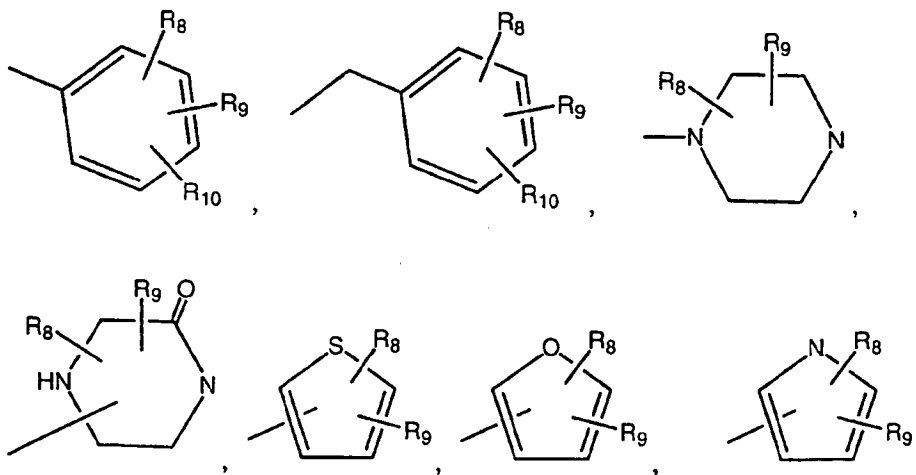


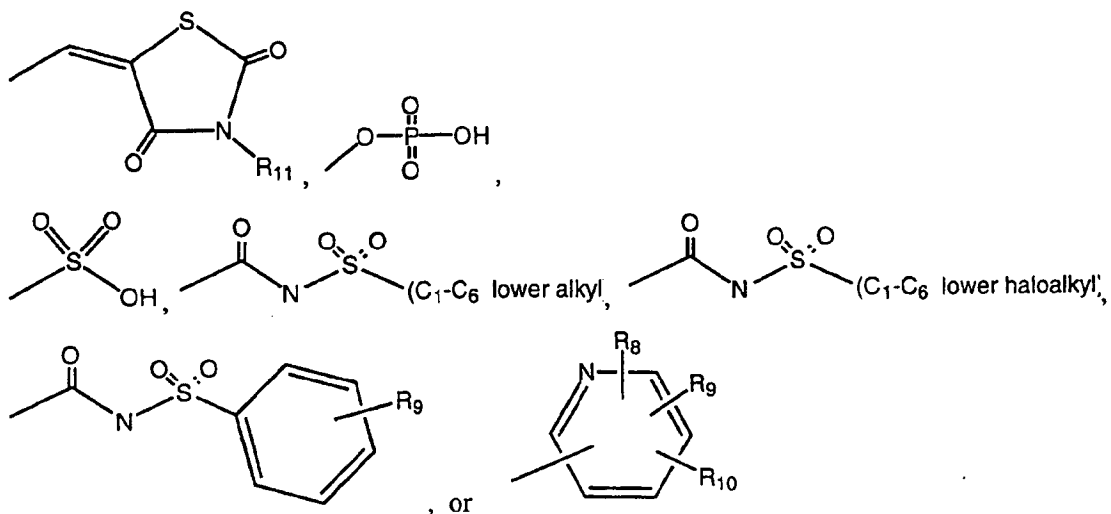


$R^{12}$  is selected from H,  $-CF_3$ ,  $C_1-C_6$  alkyl,  $-(CH_2)_n-C_3-C_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-CF_3$ ,  $-OH$ ,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,  $-NH(C_1-C_6$  alkyl), or  $-N(C_1-C_6$  alkyl) $_2$ ;

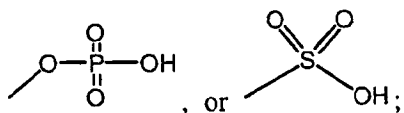
$L^1$  is selected from  $-(CH_2)_n-$ ,  $-S-$ ,  $-O-$ ,  $-C(O)-$ ,  $-C(O)-O-$ ,  $-(CH_2)_n-O-$ ,  $-(CH_2)_n-S-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-(CH_2)_n-C(O)-(CH_2)_n-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-C(Z)-N(R_6)-$ ,  $-C(Z)-N(R_6)-(CH_2)_n-$ ,  $-C(O)-C(Z)-N(R_6)-$ ,  $-C(O)-C(Z)-N(R_6)-(CH_2)_n-$ ,  $-C(Z)-NH-SO_2-$ ,  $-C(Z)-NH-SO_2-(CH_2)_n-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

$M^1$  is  $-COOH$  or a moiety selected from:



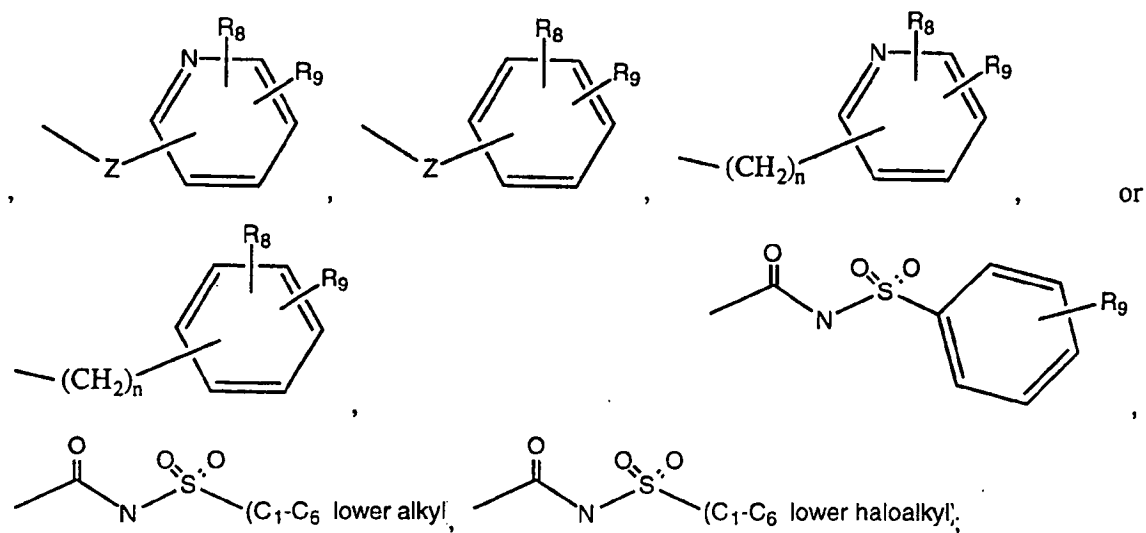


$R_8$ , in each appearance, is independently selected from H,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ , tetrazole,

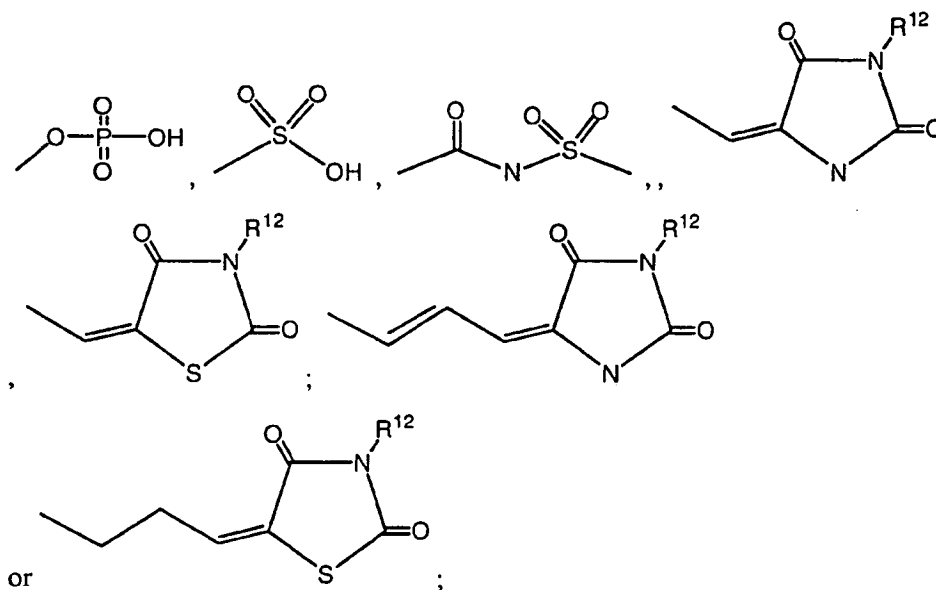


$R_9$  in each appearance is independently selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,  $-NH(C_1-C_6 \text{ alkyl})$ , or  $-N(C_1-C_6 \text{ alkyl})_2$ ;

$R^{10}$  is selected from H,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-CF_3$ ,  $-OH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,

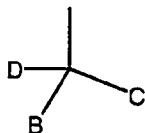


with a proviso that the moiety or combination of moieties comprising  $R_4$  include an acidic group selected from carboxylic acid, a tetrazole or a moiety of the formulae:



$R_5$  is selected from  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,

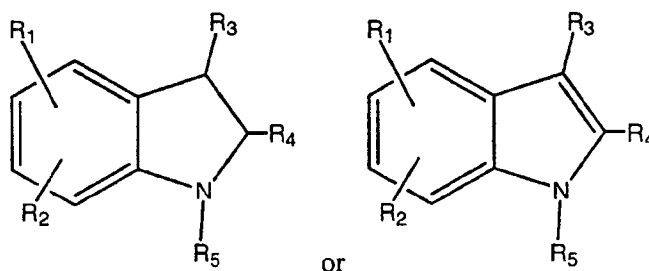
$-(CH_2)_n-S-(CH_2)_n-C_3-C_{10}$  cycloalkyl,  $-(CH_2)_n-O-(CH_2)_n-C_3-C_{10}$  cycloalkyl,  $-(CH_2)_n$ -phenyl-O-phenyl,  $-(CH_2)_n$ -phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -O-phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -phenyl-(O- $CH_2$ -phenyl)<sub>2</sub>,  $-CH_2$ -phenyl-C(O)-benzothiazole or a moiety of the formulae  $-(CH_2)_n-A$ ,  $-(CH_2)_n-S-A$ , or  $-(CH_2)_n-O-A$ , wherein A is the moiety:



D is H, C<sub>1</sub>-C<sub>6</sub> lower alkyl, C<sub>1</sub>-C<sub>6</sub> lower alkoxy, -CF<sub>3</sub> or  $-(CH_2)_n-CF_3$ ;

B and C are independently selected from phenyl, pyridinyl, pyrimidinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen, -CN, -CHO, -CF<sub>3</sub>, -OH, -C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NH<sub>2</sub> or -NO<sub>2</sub>; or a pharmaceutically acceptable salt thereof.

Yet other preferred compounds include those having the formula:



wherein

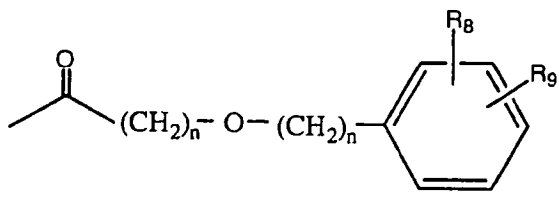
R<sub>1</sub> is selected from H, halogen, -CF<sub>3</sub>, -OH, -C<sub>1</sub>-C<sub>10</sub> alkyl, preferably -C<sub>1</sub>-C<sub>6</sub> alkyl, -S-C<sub>1</sub>-C<sub>10</sub> alkyl, preferably -S-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-benzyl, -S-benzyl; or furan, pyrrole, or thiophene, bonded to the indole ring by a chemical bond or a -S-, -O- or  $-(CH_2)_n$ - bridge, the phenyl, benzyl, furan, pyrrole, or thiophene rings being optionally substituted by from 1 to 3 substituents selected

from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy, - $NO_2$ , - $NH_2$ , -CN, - $CF_3$ ; or

$n$  is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2;

$R_2$  is selected from H, halogen, -CN, -CHO, - $CF_3$ , -OH,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy, -CHO, -CN, - $NO_2$ , - $NH_2$ , - $NH$ - $C_1$ - $C_6$  alkyl, - $N$ ( $C_1$ - $C_6$  alkyl) $_2$ , - $N$ - $SO_2$ - $C_1$ - $C_6$  alkyl, or - $SO_2$ - $C_1$ - $C_6$  alkyl;

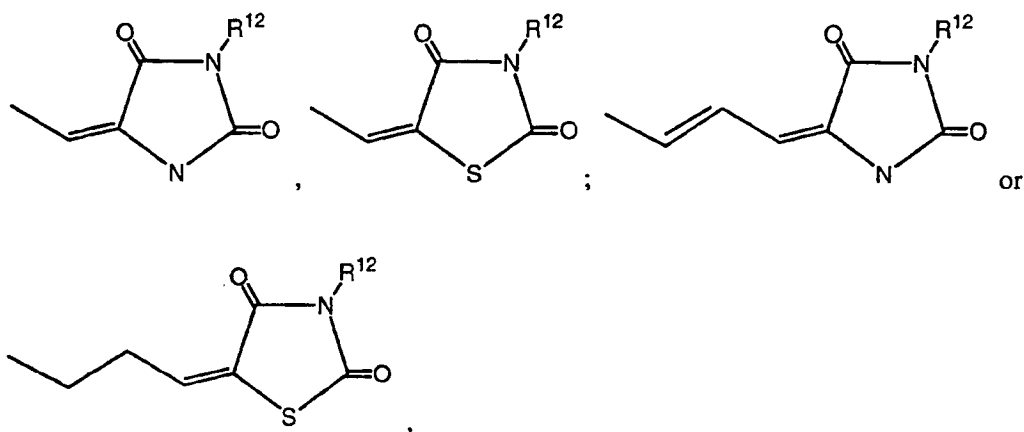
$R_3$  is selected from H, halogen, - $CF_3$ , -OH, - $C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy, -CHO, - $C(O)CH_3$ , - $C(O)-(CH_2)_nCF_3$ , -CN, - $NO_2$ , - $NH_2$ , - $NH$ - $C_1$ - $C_6$  alkyl, - $N$ ( $C_1$ - $C_6$  alkyl) $_2$ , - $N$ - $SO_2$ - $C_1$ - $C_6$  alkyl, - $SO_2$ - $C_1$ - $C_6$  alkyl, phenyl, phenyloxy, benzyl, benzyloxy- $C(O)$ -phenyl, - $C(O)$ -benzyl, - $CH_2$ -( $C_3$ - $C_5$  cycloalkyl), - $C(O)$ -OH,  $C(O)$ - $C_1$ - $C_6$  alkyl, - $C(O)$ -O- $C_1$ - $C_6$  alkyl, - $C(O)$ - $CF_3$ , or - $(CH_2)_n$ -S- $CH_2$ -( $C_3$ - $C_5$  cycloalkyl), the rings of the relevant  $R_3$  groups being optionally substituted by from 1 to 3 groups selected from halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, - $NO_2$ , - $CF_3$ , - $C(O)$ -OH, or -OH; or a moiety of the formula:



$n$  in each appearance is independently selected as an integer selected from 0-3;

$R^8$  and  $R^9$  are independently selected in each appearance from H, -COOH, - $(CH_2)_n$ -COOH, - $(CH_2)_n$ - $C(O)$ -COOH, - $CF_3$ , -OH, - $(CH_2)_n$ - $C(O)$ -COOH, - $C_1$ - $C_6$  alkyl, -O- $C_1$ - $C_6$  alkyl, - $NH$ ( $C_1$ - $C_6$  alkyl), or - $N$ ( $C_1$ - $C_6$  alkyl) $_2$ ;

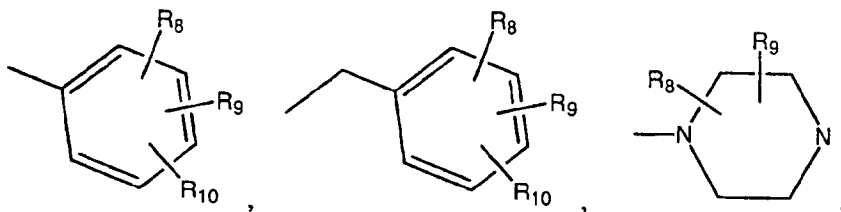
$R_4$  is selected from -COOH, - $(CH_2)_n$ -COOH, - $(CH_2)_n$ - $C(O)$ -COOH, -CH=CH-COOH, tetrazole, - $(CH_2)_n$ -tetrazole, the moiety - $L^1$ - $M^1$  or a moiety of the formulae:



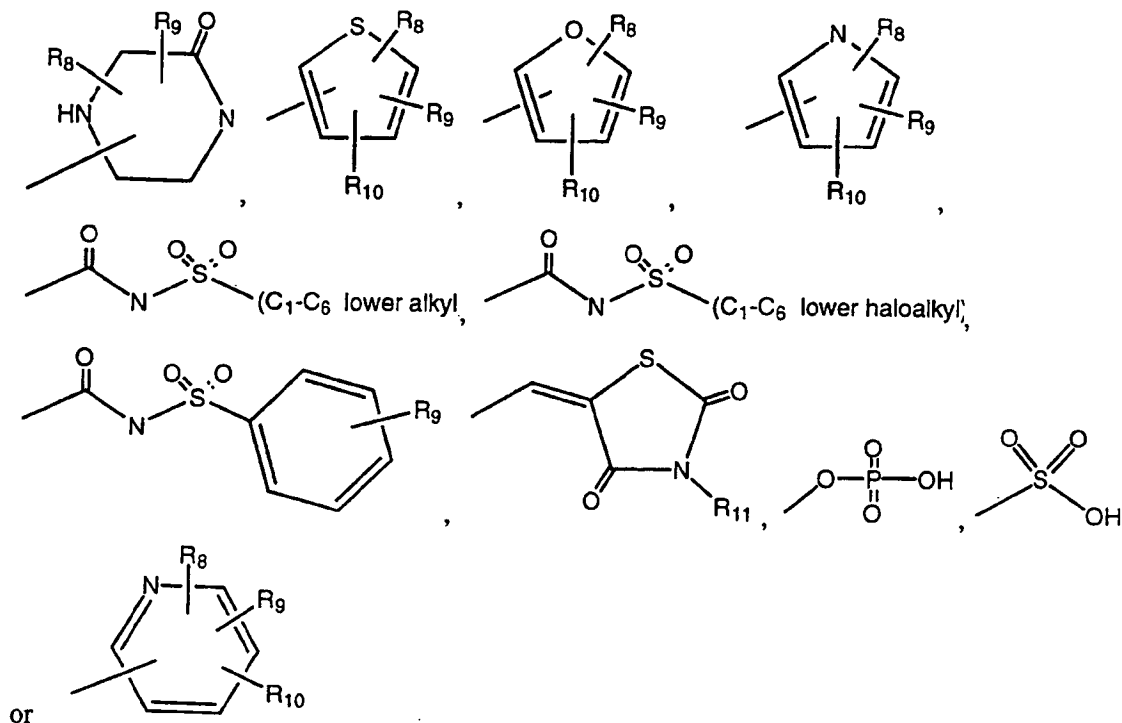
$R^{12}$  is selected from H,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $-(\text{CH}_2)_n\text{-C}_3\text{-C}_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C(O)-COOH}$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $-\text{O-C}_1\text{-C}_6$  alkyl,  $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ ;

$L^1$  is selected from  $-(\text{CH}_2)_n-$ ,  $-\text{S}-$ ,  $-\text{O}-$ ,  $-\text{C(O)}-$ ,  $-\text{C(O)-O-}$ ,  $-(\text{CH}_2)_n\text{-O-}$ ,  $-(\text{CH}_2)_n\text{-S-}$ ,  $-(\text{CH}_2)_n\text{-O-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-C(O)-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-O-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n-$ ,  $-\text{C(Z)-N(R}_6)-$ ,  $-\text{C(Z)-N(R}_6)-(CH_2)_n-$ ,  $-\text{C(O)-C(Z)-N(R}_6)-$ ,  $-\text{C(O)-C(Z)-N(R}_6)-(CH_2)_n-$ ,  $-\text{C(Z)-NH-SO}_2-$ ,  $-\text{C(Z)-NH-SO}_2-(CH_2)_n-$ ,  $-\text{C(O)-(CH}_2)_n\text{-O-}$ ,  $-\text{C(O)-N-}$ , or  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n\text{-C(O)-N-}$ ;

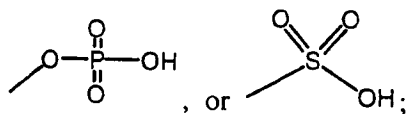
$M^1$  is  $-\text{COOH}$  or a moiety selected from:





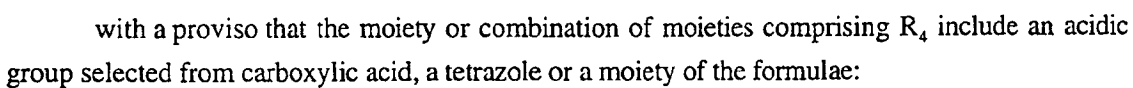


$R_8$ , in each appearance, is independently selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ , tetrazole,

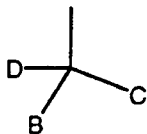


$R_9$  in each appearance is independently selected from H, halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,  $-\text{NH}(\text{C}_1-\text{C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})_2$ ;

$R_{10}$  is selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,



$R_5$  is selected from  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -S- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -O- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -phenyl-O-phenyl,  $-(CH_2)_n$ -phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -O-phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -phenyl-(O- $CH_2$ -phenyl) $_2$ ,  $-CH_2$ -phenyl-C(O)-benzothiazole or a moiety of the formulae  $-(CH_2)_n$ -A,  $-(CH_2)_n$ -S-A, or  $-(CH_2)_n$ -O-A, wherein A is the moiety:



D is H,  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-CF_3$  or  $-(CH_2)_n$ - $CF_3$ ;

B and C are independently selected from phenyl, pyridinyl, pyrimidinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen,  $-CN$ ,  $-CHO$ ,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-NH_2$  or  $-NO_2$ ; or a pharmaceutically acceptable salt thereof.

The present invention also provides for a method of inhibiting the phospholipase enzyme activity of an enzyme, comprising administering to a mammalian subject a therapeutically effective amount of a compound of the present invention. Methods of treating an inflammatory response or condition, comprising administering to a mammalian subject a therapeutically effective amount of a compound of the present invention are also provided. Pharmaceutical compositions comprising compounds of the present invention and a pharmaceutically acceptable carrier are also provided.

Pharmaceutically acceptable salts of the compounds of the compounds described herein are also part of the present invention and may be used in practicing the compounds and methods disclosed herein.

#### Brief Description of the Figures

Figs. 1-13 depict schemes for synthesis of compounds of the present invention. The depicted schemes are described in further detail below.

#### Detailed Description of Preferred Embodiments

As used herein, the terms "aryl" and "substituted aryl" are understood to include monocyclic, particularly including five- and six-membered monocyclic, aromatic and heteroaromatic ring moieties and bicyclic aromatic and heteroaromatic ring moieties, particularly including those having from 9 to 10 ring atoms. Among these aryl groups are understood to be phenyl rings, including those found in phenoxy, benzyl, benzyloxy, biphenyl and other such moieties. The aryl and heteroaryl groups of this invention also include the following:

- a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, or oxathiazole; or
- b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadiazine, oxazine, or morpholine; or
- c) a bicyclic ring moiety optionally containing from 1 to 3 ring heteroatoms

selected from N, S or O including, but not limited to benzofuran, chromene, indole, isoindole, indoline, isoindoline, naphthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine, quinazoline, cinnoline, phthalazine, or naphthyridine.

The "substituted aryl" groups of this invention include such moieties being optionally substituted by from 1 to 3 substituents selected from halogen, C1-C10 alkyl, preferably C1-C6 alkyl, C1-C10 alkoxy, preferably C1-C6 alkoxy, -CHO, -COOH or esters thereof, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH or combinations thereof, such as -CH<sub>2</sub>CF<sub>3</sub>, -NH(CH<sub>3</sub>), etc.

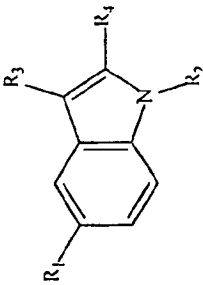
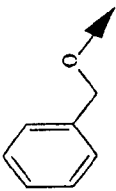
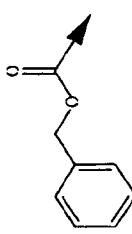
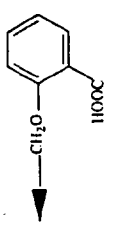
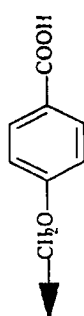
A preferred subset of these groups, optionally substituted as just described, include moieties formed from benzene, pyridine, naphthylene or quinoline rings. A further preferred group includes those of furan, pyrrole, thiophene, pyrimidine, and morpholine rings. A preferred group of bicyclic aromatic groups includes benzofuran, indole, naphthalene, and quinoline rings.

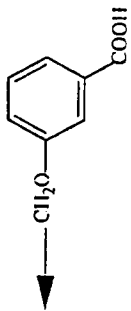
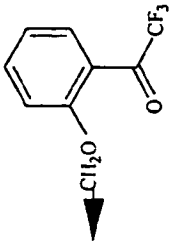
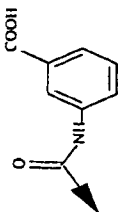
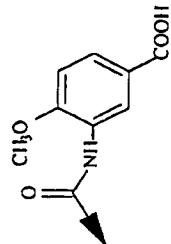
The alkyl, alkenyl and alkynyl groups referred to herein indicate such groups having from 1 to 10, preferably 1 to 6 carbon atoms, and may be straight, branched or cyclic. Unless indicated otherwise, it is preferred that these groups be straight or branched. Halogens herein are understood to include F, Cl, Br and I.

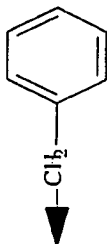
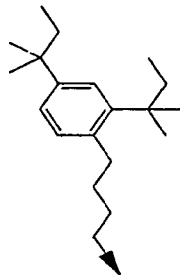
Preferred compounds of the present invention are disclosed in Tables I-VI below. Methods for synthesis of the compounds listed in Tables I-VI are described below. Compound Nos. in the tables correspond to example numbers below describing synthesis of that particular compound.

Tables I-VI also report data for the listed compounds in the "LysoPC" assay and the Coumarine assay (see Example 88 below). In the data columns of the tables, assay results are reported as an "IC<sub>50</sub>" value, which is the concentration of a compound which inhibits 50% of the activity of the phospholipase enzyme in such assay. Where no numerical IC<sub>50</sub> value appears, "NA" denotes that inhibitory activity was not detected from such compound in the corresponding assay and a blank box denotes that the compound was not tested in such assay as of the time of filing of the present application.

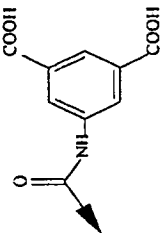
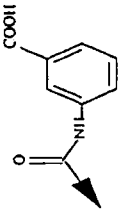
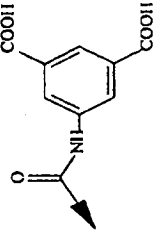
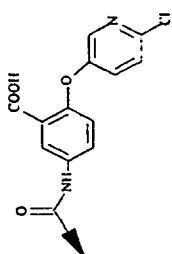
Table I

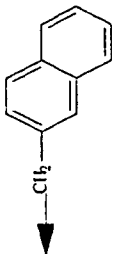
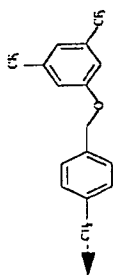
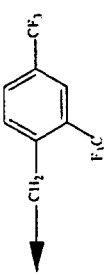
						
No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	IC <sub>50</sub> (μM)	
					Lyso PC	Cou-marine
1			-H		47	
2					6	

14		52	6
6.5	NA	4.3	2.0
			

	
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3	4	5	6
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15	3.8	6.5	28
2.1	0.11	0.081	0.33
			

		
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7	8	9	10
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11	12	13	14	15
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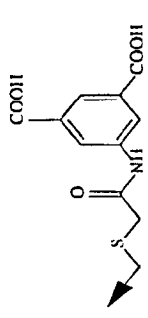
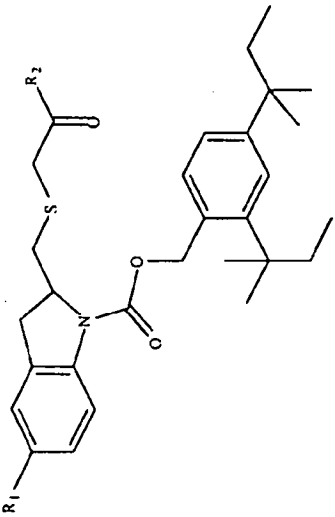
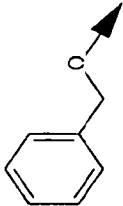
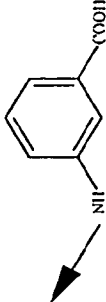
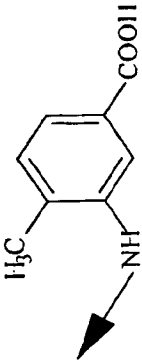
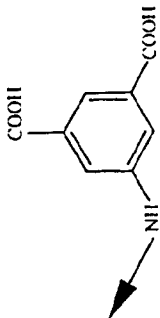
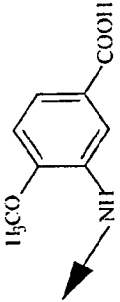
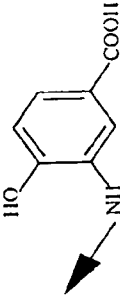
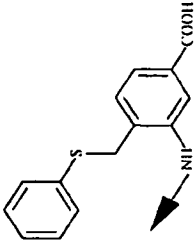
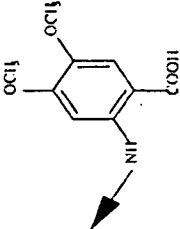
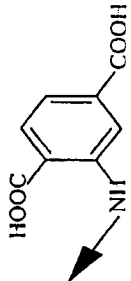
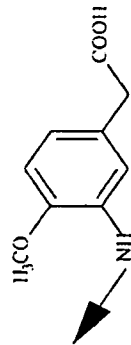
50	
6.5	
16	

Table II

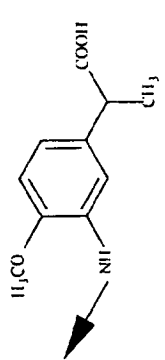
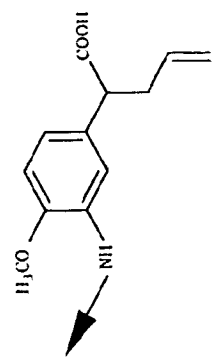
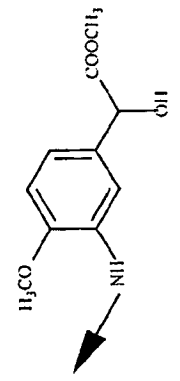
	No.	R <sub>1</sub>		R <sub>2</sub>		IC <sub>50</sub> (μM)	
	17					Lyso PC	Cou- marine
						0.32	6

	0.28	10
	0.21	4
	0.28	9
	0.29	4.5

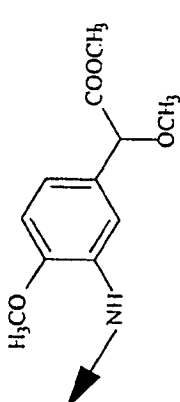
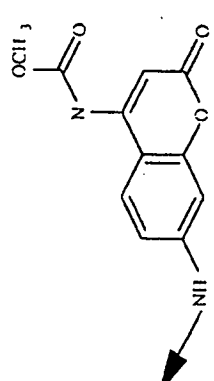
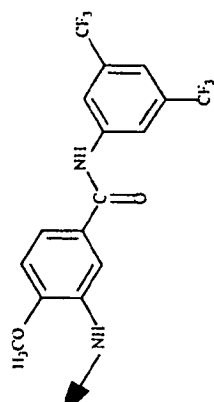
18	19	20	21
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	0.10	5
	0.95	5
	1.6	2.5
	1.3	10

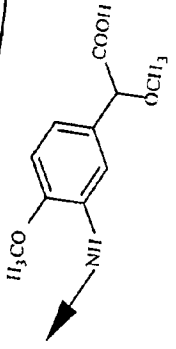
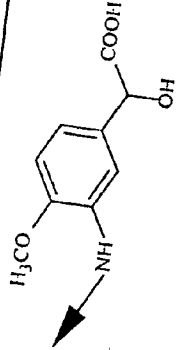
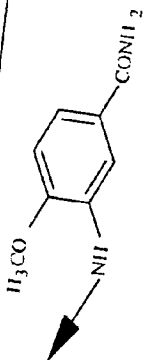
22	23	24	25
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18	1.2	
13	2.3	
-	-	

26	27	28
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--	28	44
		

29	30	31
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	3.8	5
	2.6	5
	24	> 50

32	33	34
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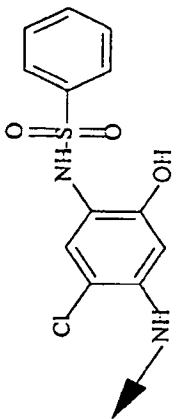
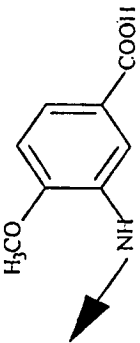
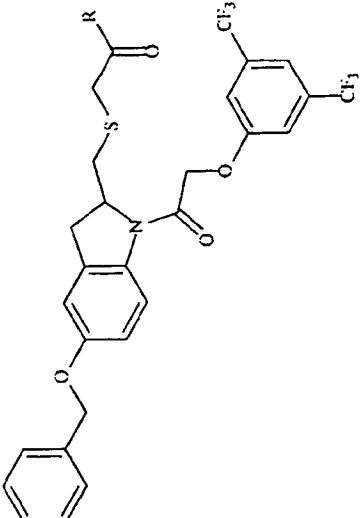
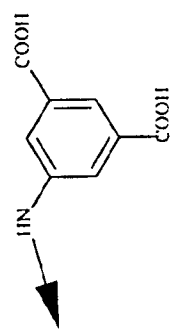
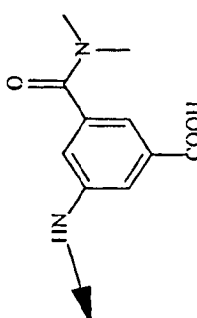
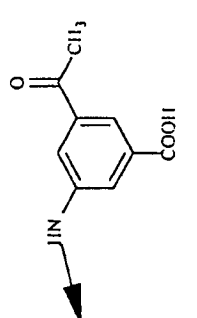
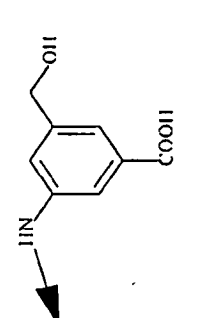
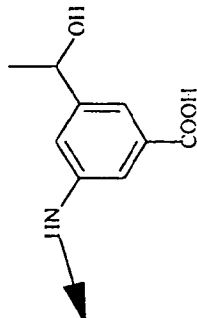
35			9.1	28
36	-H		2.3	4

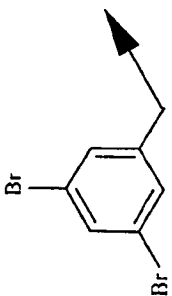
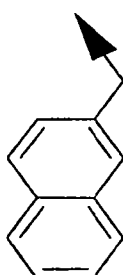
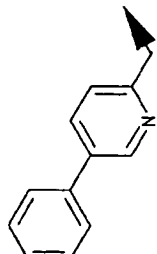
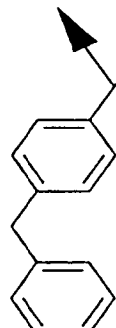
Table III

No.	R	IC <sub>50</sub> (μM)	
		Lyso PC	Cou-marine
			
37	-OH	7.6	> 30
38		6.9	> 50

18	4.3		39
11	6.2		40
22	2.2		41
14	7.8		42

54Table IV

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45		0.37	5
46		0.71	10
47		1.6	16
48		0.3	5.5
49	CH <sub>3</sub> -	40	> 50

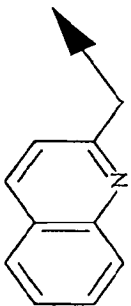
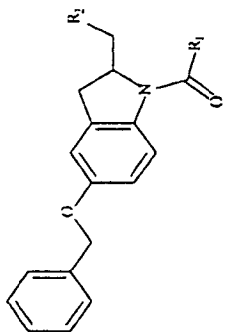
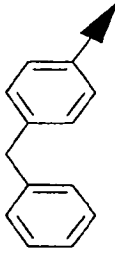
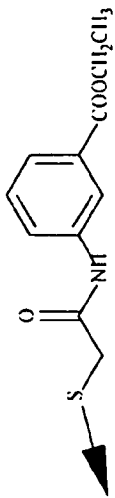
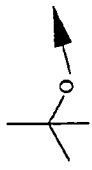
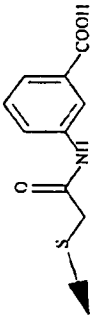

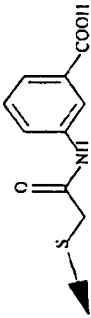
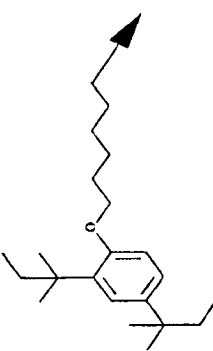
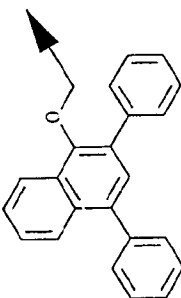
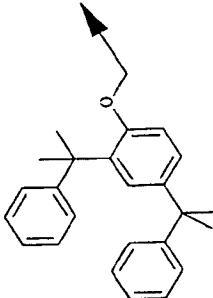
> 50	
4.4	
	
50	

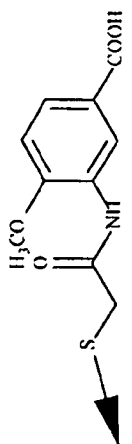
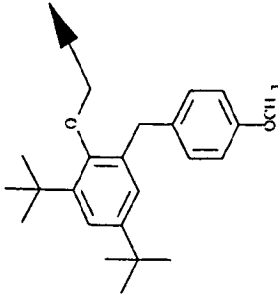
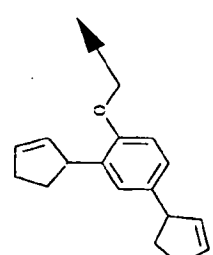
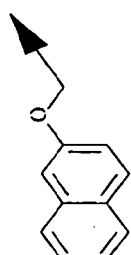
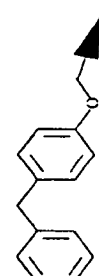
Table V

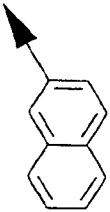
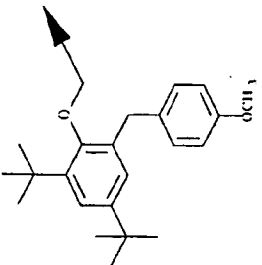
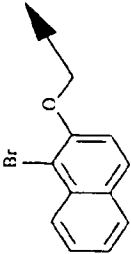
No.	R <sub>1</sub>	R <sub>2</sub>	IC <sub>50</sub> (μM)	
			Lyso PC	Coumarine
			36	
			8.0	26
			15	>64


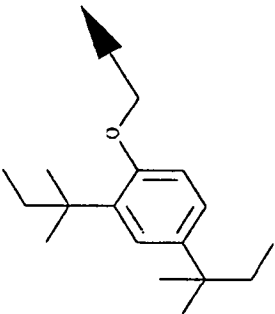
14	12	5
0.23	0.45	0.47

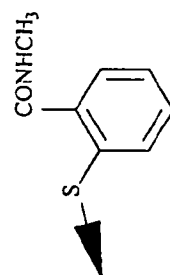
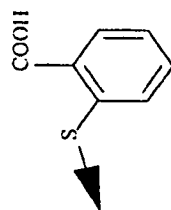
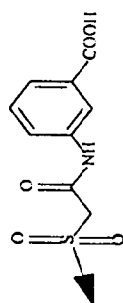
		
54	55	56



8	4	>30	>30
0.26	0.56	8.7	4.6
			
57	58	59	60
			

12.1	1.7	
>20	8	
		
61	62	63

64				17.6	> 64
65	$\text{CH}_3(\text{CH}_2)_3\text{O}-$				
66				2.3	6
67				0.22	10
68				> 50	> 50



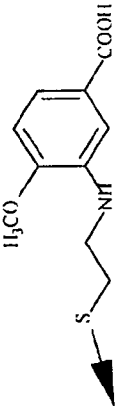
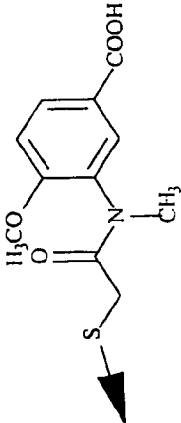
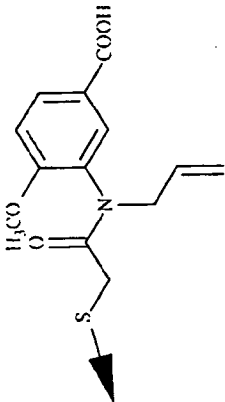
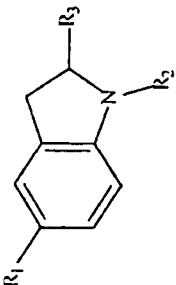
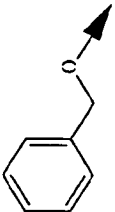
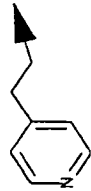
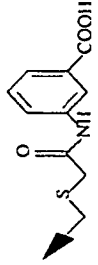
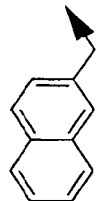
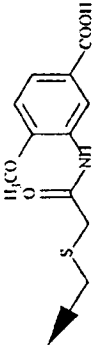
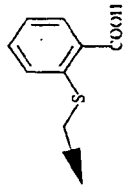
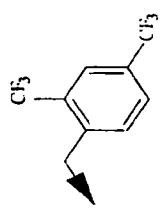
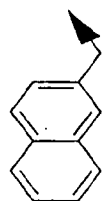
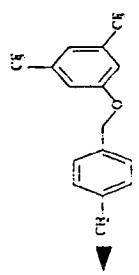
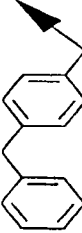
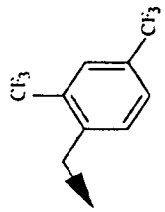
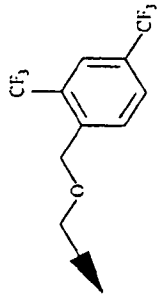
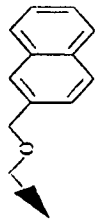
69	6	19.4	
70	19	0.84	
71	12	5.9	

Table VI

				
No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	IC <sub>50</sub> (μM) Lyso PC      Cou- marine
72				> 64
73				1.9      6

1.1	5		
7.0	6.2		
	4.5		
	2.5		
			
			
			

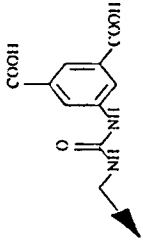
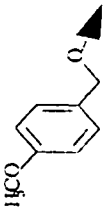
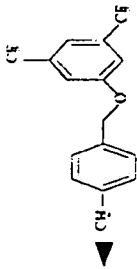
74	75	76	77
----	----	----	----

3	4.2	16	15
			3.2
			

78	79	80	81
----	----	----	----

82				0.1	15
83	H-			> 50	> 50
84				23	> 50
85				21	> 50



17	6.5	
86	87	 

Compounds of the present invention were also tested for *in vivo* activity in a rat paw edema test according to the procedure described in Example 89. The results are reported in Table VII.

5 Table VII

10	Compound No.	% inhibition of rat carrageenan-induced footpad edema
15	8	29
	10	8.9
	14	34.2
	15	21.8
	16	26.3
	17	29.3
	19	10.5
	20	19.5
20	25	17.5
	26	10.3
	32	26.7
	33	4.2
	46	12.5
	47	7.8
25	50	11.7
	67	17.5
	70	21.7
	76	8.2
	77	13.0

As used herein, "phospholipase enzyme activity" means positive activity in an assay for metabolism of phospholipids (preferably one of the assays described in Example 88 below). A compound has "phospholipase enzyme inhibiting activity" when it inhibits the activity of a phospholipase (preferably cPLA<sub>2</sub>) in any available assay (preferably an assay described below in Example 88 or Example 89) for enzyme activity. In preferred embodiments, a compound has (1) an IC<sub>50</sub> value of less than about 25  $\mu$ M, preferably less than about 6  $\mu$ M, in the LysoPC assay; (2) an IC<sub>50</sub> value of less than about 50  $\mu$ M in the vesicle assay; (3) an IC<sub>50</sub> value of less than about 1  $\mu$ M in the PMN assay; (4) an IC<sub>50</sub> value of less than about 15  $\mu$ M in the Coumarine assay; and/or (5) measurable activity (preferably at least about 5% reduction in edema, more preferably at least about 10% reduction, more preferably at least about 15%, most preferably about 20-30%) in the rat carrageenan-induced footpad edema test.

Compounds of the present invention are useful for inhibiting phospholipase enzyme (preferably cPLA<sub>2</sub>) activity and, therefore, are useful in "treating" (i.e., treating, preventing or ameliorating) inflammatory or inflammation-related responses or conditions (e.g., rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disease, and other diseases mediated by prostaglandins, leukotrienes or PAF) and other conditions, such as osteoporosis, colitis, myelogenous leukemia, diabetes, wasting and atherosclerosis.

The present invention encompasses both pharmaceutical compositions and therapeutic methods of treatment or use which employ compounds of the present invention.

Compounds of the present invention may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to a compound or compounds of the present invention and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition may further contain other anti-inflammatory agents. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with compounds of the present invention, or to minimize side effects caused by the compound of the present invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which compounds of the present invention are combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of an inflammatory response or condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of a compound of the present invention is administered to a mammal having a condition to be treated. Compounds of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing other anti-inflammatory agents, cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more other anti-inflammatory agents, cytokines, lymphokines or other hematopoietic factors, compounds of the present invention may be administered either simultaneously with the other anti-inflammatory agent(s), cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering compounds of the present invention in combination with other anti-inflammatory agent(s), cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of compounds of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, or cutaneous, subcutaneous, or intravenous injection.

5           When a therapeutically effective amount of compounds of the present invention is administered orally, compounds of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% compound of the  
10           present invention, and preferably from about 25 to 90% compound of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain  
15           physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of compound of the present invention, and preferably from about 1 to 50% compound of the present invention.

          When a therapeutically effective amount of compounds of the present invention is  
20           administered by intravenous, cutaneous or subcutaneous injection, compounds of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition  
25           to compounds of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

30           The amount of compound(s) of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone.

Ultimately, the attending physician will decide the amount of compound of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of compound of the present invention and observe the patient's response. Larger doses of compounds of the present invention may be administered until the  
5 optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.1  $\mu$ g to about 100 mg (preferably about .1 mg to about 50 mg, more preferably about 1mg to about 2 mg) of compound of the present invention per kg body weight.

10 The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the compounds of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending  
15 physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

#### Methods of Synthesis for Examples 1-87

Compounds of the present invention can be prepared according to the following  
20 methods. Temperatures are in degrees Celsius.

#### METHOD A

Indol-2-carboxylic acid ethyl ester I is converted to aldehyde II in two steps: reduction with lithium aluminum hydride (LAH) or other hydride in a suitable solvent such as  
25 tetrahydrofuran (THF) at 0°C, and then oxidation with an oxidizing reagent such as manganese dioxide in a solvent such as THF. Deprotonation of aldehyde II with a strong base such as potassium hexamethyldisilyl amide (KHMDs) in THF, followed by reaction with a chloroformate in the presence of a base, such as triethyl amine, produces carbamate III. III is transformed into bromide IV in two steps: (1) reduction with sodium borohydride  
30 in an alcoholic solution and (2) reaction with carbon tetrabromide in the presence of a phosphine reagent such as bis(diphenylphosphino)propane in dichloromethane. Displacement of the bromine in IV with potassium phenoxide, prepared by reaction of a phenol with

KHMDS, in a suitable solvent such as THF or DMF affords ether V. V can be converted to either trifluoromethyl ketone VII or to carboxylic acid IX in different procedures. Reaction of V with trifluoromethyl trimethylsilane (TMSCF<sub>3</sub>) in the presence of tetrabutylammonium fluoride gives trifluoromethyl alcohol, which is then oxidized with periodinane (Dess-Martin reagent) in dichloromethane to afford ketone VI. In this stage the carbamate can be removed with either trifluoroacetic acid (TFA) or with a base such as sodium hydroxide. The indole nitrogen is then alkylated with a suitable alkyl bromide in the presence of a base such as sodium hydride to produce VII. Alternatively, V can be deprotected with TFA or aqueous base, and then reacted with alkyl bromide to give VIII, which is oxidized with sodium chlorite in an aqueous THF to yield acid IX.

#### METHOD B

2-Indolyl carboxylic acid ethyl ester I is deprotonated with a strong base such as sodium hydride (NaH) in THF, and then reacted with a suitable alkyl bromide to give X. Hydrolysis of X with an aqueous base such as sodium hydroxide and reaction with aniline or a substituted aniline in the presence of a carbodiimide such as dimethylaminopropyl ethylcarbodiimide hydrochloride (EDCI) in a suitable solvent such as dichloromethane affords amide XI. XI is hydrolyzed to corresponding acid XII in an aqueous base such as sodium hydroxide.

#### METHOD C

Indole I can be brominated on the 3-position by reaction with a bromine or N-bromosuccinimide in a suitable solvent such as carbon tetrachloride or dichloromethane to yield bromide XIII. Reaction of XIII with a suitable alkyl bromide in the presence of a strong base such as NaH in THF or DMF affords indole XIV. Palladium mediated coupling of XIV with a suitable alkene in the presence of phosphine and a base such as triethyl amine produces 3-substituted indole XV. XV can be converted to amide XVII in two step reactions: (1) hydrolysis with aqueous base such as NaOH and (2) coupling with an amine in the presence of carbodiimide such as EDCI. Ester XIV can be transformed to lithium salt XVIII

by hydrolysis with aqueous base and then reaction with lithium hydroxide in a suitable solvent such as ether. Lithiation with n-butyl lithium in a suitable solvent such as THF, and then acylation with an acyl chloride in THF affords ketone XIX. Carbodiimide (EDCI) catalyzed coupling of XIX and a suitable amine gives amide XX.

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#### METHOD D

Indole I can be converted to XXI in two steps: (1) reduction with LAH in a solvent such as THF and (2) silylation with t-butyldimethylsilyl chloride (TBDMSCl) in a solvent such as dichloromethane or DMF in the presence of a base such as imidazole. Treatment of XXI with Grignard reagent such as ethyl magnesium bromide in a solvent such as THF at -60°C, acylation of the resulting magnesium salt with a suitable acyl chloride such as acetyl chloride in ether and finally, alkylation on the nitrogen with an alkyl halide such as ethyl bromide in the presence of a strong base such as NaH in DMF affords ketone XXII. The silyl group on XXII is removed using tetrabutylammonium fluoride in a solvent such THF, the resulting alcohol is then converted to bromide using carbon tetrabromide and bis(diphenylphosphino)ethane in a solvent such as dichloromethane to yield bromide XXIII. Displacement of the bromine of XXIII with a thiol compound in the presence of a base such as Cs<sub>2</sub>CO<sub>3</sub>, or with an alcohol in the presence of a strong base such as NaH in DMF affords XXIV (sulfide, or ether respectively).

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#### METHOD E

Aldehyde II, prepared by Method A, can be alkylated by a suitable alkyl bromide (or iodide), such as benzyl bromide or ethyl iodide in the presence of a strong base such as sodium hydride or KHMDS in a solvent such as DMF to yield XXV. XXV can be converted to an unsaturated acid XXVI by two steps: (1) Wittig reaction with a suitable reagent such as trimethyl phosphonoacetate in the presence of a base such as sodium hydride in a solvent such as THF and (2) Hydrolysis by aqueous sodium hydroxide. Coupling reaction of XXVI with an amine catalyzed by a diimide such as EDCI (dimethylaminopropyl ethylcarbodiimide

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hydrochloride), followed by hydrolysis with aqueous base such as sodium hydroxide affords XXVII.

#### METHOD F

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Indole I is reduced with LAH in a solvent such as THF. A second reduction with sodium cyanoborohydride in a solvent such as acetic acid to yield alcohol XXVIII. Protection of the nitrogen of XXVIII with t-butoxycarbonyl (BOC) using di-t-butylidicarbonate ((BOC)<sub>2</sub>O) in the presence of a base such as triethylamine affords carbamate XXIX. The hydroxyl group in XXIX is mesylated using mesyl chloride and triethylamine in a solvent such as dichloromethane, and then displaced by either a thiol or an alcohol as described in METHOD D to produce indoline XXX. Deprotection of XXX using trifluoroacetic acid affords XXXI, which is either acylated (acyl chloride, triethylamine, dichloromethane) or alkylated (alkyl halide, K<sub>2</sub>CO<sub>3</sub>, DMF) to afford XXXII, or XXXIII respectively.

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#### METHOD G

Carboxylic acid XXXIV is converted to aldehyde XXXV in two steps: (1) reaction with N,O-dimethylhydroxy amine in the presence of EDCI in a solvent such as dichloromethane, and (2) reduction with diisobutyl aluminum hydride (DIBAL) in a solvent such as THF. Treatment of XXXV with trimethyl phosphonoacetate in the presence of a strong base such as KHMDs in a solvent such as THF results in the formation of ester XXXVI. Reduction of XXXVI with tin in hydrogen chloride, followed by cyclization in a heated inert solvent such as toluene gives XXXVII. Alkylation on nitrogen of XXXVII under conditions described in METHOD F, and then hydrolysis of the ester with aqueous base such as NaOH affords acid XXXVIII. XXXVIII can be converted to an amide XXXIX by coupling with a suitable amine such as benzylamine in the presence of EDCI.

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#### METHOD H

Aldehyde XXXV, prepared in METHOD G, is subjected to a Wittig reaction using methyl triphenylphosphonium iodide in the presence of a strong base such as KHMDS or NaH in a solvent such as THF to afford alkene XL. Reduction of the nitro group of XL with iron powder in an ammonium chloride solution, followed by treatment with benzyl chloroformate in the presence of a base such as triethyl amine produces carbamate XLI. XLI is treated with iodine in a basic solution such as aqueous NaHCQ in THF to yield iodide XLII. Displacement of the iodine on XLII with lithium benzoate in a solvent such as DMF, followed by hydrolysis with NaOH affords alcohol XLIII.

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#### METHOD I

Indoline XXVIII, prepared in METHOD F or METHOD H, can be either acylated by reaction with an acyl chloride in the presence of a base such as triethyl amine or alkylated using alkyl halide in the presence of  $K_2CO_3$  in a solvent such as DMF to produce alcohol XLIV. Treatment of XLIV with mesyl chloride and triethyl amine in a solvent such as dichloromethane, followed by displacement with a thiol such as methyl mercaptoacetate in the presence of a base such as  $Cs_2CO_3$  in a solvent such as acetonitrile yields ester XLV. Hydrolysis of XLV with an aqueous base such as NaOH gives acid XLVI, which can be coupled with an amine catalyzed by a diimide such as EDCI in a solvent such as dichloromethane to afford amide XLVII. XLVII can be alkylated on the amide nitrogen by treatment with alkyl halide and strong base such as NaH in DMF. Hydrolysis of the resulting amide with aqueous base such as NaOH gives acid XLIX. XLIV can also be directly hydrolyzed with NaOH to a carboxylic acid XLVIII.

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#### METHOD J

METHOD J illustrates the synthesis of alpha-substituted aminophenylacetic acid esters. Ester L can be deprotonated with a strong base such as lithium diisobutylamide (LDA) in a solvent such as THF, and subsequently alkylated with an alkyl halide such as methyl iodide to give LI. Reduction of LI to amine LIII can be accomplished using hydrogenation catalyzed by

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palladium in a solvent such as ethanol. L can be oxidized to alcohol LII using LDA and oxaziridine in a solvent such as THF. Alkylation of LII with a alkylating reagent such as methyl iodide in the presence of a strong base such as NaH in DMF, followed by catalytic hydrogenation in the presence of palladium produces amine LIV.

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#### METHOD K

METHOD K illustrates the synthesis of substituted aminobenzoic acid esters. Mono-acid LV  
10 can be converted to amide LVI by the following steps: (1) reaction with oxalyl chloride in dichloromethane to form acid chloride and (2) treatment with a suitable amine such as dimethyl amine. Reduction of the nitro group to the amine is accomplished with hydrogenation catalyzed by palladium as described in METHOD J. LV can be reduced to alcohol LVIII with hydroborane-THF complex in THF. Protection of the hydroxy group as a  
15 silyl ether using TBDMSCl in the presence of imidazole and subsequently, reduction of the nitro group ( $H_2$  / Pd-C) to the amine affords LIX. LVIII can be converted to the secondary alcohol LX in two steps: (1) oxidation with a suitable reagent such as manganese dioxide ( $MnO_2$ ) in ethyl acetate and (2) addition of a desired Grignard reagent such as methyl magnesium bromide in THF. Oxidation of LX with  $MnO_2$  in THF and reduction of the nitro  
20 group ( $H_2$  / Pd-C) produces ketone LXIII. Reduction of LVII ( $H_2$  / Pd-C) yields LXI.

#### METHOD L

25 Alcohol LXIV, prepared in METHOD I, can be debenzylated by hydrogenolysis catalyzed by palladium on carbon in a solvent such as ethanol. The resulting alcohol is treated with p-methoxybenzyl chloride in the presence of  $K_2CO_3$  in a solvent such as THF to afford LXV. Alcohol LXV can be transformed into ether or sulfide LXVI by the procedures described in METHOD D. Deprotection of the p-methoxybenzyl group with TFA in a solvent such as  
30 dichloromethane, and subsequent alkylation on oxygen with a suitable reagent such as 4-benzylbenzyl bromide in the presence of  $K_2CO_3$  in a solvent such as THF affords LXVII.

EXPERIMENTAL SECTION

The Examples which follow further illustrate the invention. All temperatures set forth in the Examples are in degrees Celsius. All the compounds were characterized by proton magnetic resonance spectra taken on a Varian Gemini 300 spectrometer or equivalent instruments.

EXAMPLE 1

2-(2-(1-Phenylmethoxycarbonyl-5-phenylmethoxy)indolyl)methoxybenzoic acid

Step 1: 2-(5-Phenylmethoxy)indolyl aldehyde

12.3 g (42 mmol) of ethyl 2-(5-phenylmethoxy)indolyl carboxylate was dissolved in 100 mL of THF, to which was added 130 mL (130 mmol) of 1 M solution of lithium aluminum hydride in THF at 0°C. The reaction was stirred at this temperature for 2 hours and quenched by adding 65 mL of 6 N NaOH solution slowly. The product was extracted with ethyl acetate, and the organic phase was washed with aqueous ammonium chloride. Evaporation of the solvent afforded crude alcohol, which without further purification was dissolved in 400 mL of THF, 52 g of manganese(IV) oxide was added, and the mixture was stirred at room temperature overnight. Removal of manganese oxide by filtration and flash chromatographic purification using 3:1 hexane:ethyl acetate yielded 8.15 g of the title compound.

Step 2: Benzyl (1-(2-formyl-5-phenylmethoxy)indolyl)formate

To a solution of 6.9 g (27.5 mmol) of the aldehyde of step 1 in 140 mL of THF was slowly added 61 mL (30.5 mmol) of 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene at -35°C. After stirring at this temperature for 10 min, 4.4 mL (29.5 mmol) of benzyl chloroformate was added at -35°C, and the mixture was then warmed from -35°C to 0°C for 3.5 hours. The reaction was quenched by pouring into aqueous ammonium chloride.

Aqueous work up and flash chromatography using 12:1 toluene:ethyl acetate afforded 4.8 g of the title compound.

Step 3: Benzyl (1-(2-hydroxymethyl-5-phenylmethoxy)indolyl)formate

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To a solution of 2.9 g (7.5 mmol) of the aldehyde of step 2 in 40 mL of THF and 20 mL of trifluoroethanol was added 760 mg (20 mmol) of sodium borohydride at 0°C. The mixture was stirred at 0°C for 30 min and then quenched by adding aqueous ammonium chloride. Flash chromatography using 2:1 hexane-ethyl acetate afforded 2.2 g of the title compound.

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Step 4: Benzyl (1-(2-bromomethyl-5-phenylmethoxy)indolyl)formate

To a solution of 2.2 g (5.7 mmol) of the alcohol of step 3 and 2.05 g (5.0 mmol) of 1,3-bis(diphenylphosphino)propane in 60 mL of dichloromethane was added a solution of 2.0 g (6 mmol) of carbon tetrabromide in 4 mL of dichloromethane at 15°C. The mixture was stirred at room temperature for 2 hours and 1 g (3 mmol) of 1,3-bis(diphenylphosphino)propane was added at room temperature. After 1 hour stirring, the reaction was quenched by adding aqueous ammonium chloride. Aqueous work up and flash chromatography using 4:1 hexane:ethyl acetate afforded 1.7 g of the title compound.

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Step 5: Benzyl (1-(2-(2-formylphenoxy)methyl-5-phenylmethoxy)indolyl)formate

To a solution of 439 mg (3.6 mmol) of methyl 2-hydroxybenzoate in 18 mL of THF was added 6 mL (3 mmol) of 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene at 0°C. The solution was stirred at 0°C for 10 min, to which was added a solution of 1.25 g (2.8 mmol) of the bromide, prepared in step 4, in THF at 0°C. The reaction was warmed to room temperature and stirred at this temperature for 2 hours. After aqueous work up (NH<sub>4</sub>Cl / ethyl acetate), the organic solvent was collected, dried over sodium sulfate and evaporated. The product was solidified and washed with ethyl acetate:hexane 1:1. Yield 690 mg (51%).

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Step 6:

120 mg (0.24 mmol) of the aldehyde of step 5 was dissolved in 11 mL of 5:1:5 THF-acetonitrile-2,2-dimethylethanol. To this solution was added a solution of 56 mg (0.5 mmol) of sodium chlorite in 0.5 mL water and 1 drop of aqueous hydrogen peroxide solution. After 4 hours, another 56 mg (0.5 mmol) of sodium chlorite was added. The mixture was stirred at room temperature for three days. Aqueous work up and flash chromatography using 2.5:1:0.05 hexane:ethyl acetate-acetic acid afforded 110 mg of the title compound.

#### EXAMPLE 2

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4-(2-(1-Phenylmethoxycarbonyl-5-phenylmethoxy)indolyl)methoxybenzoic acid

The title compound was prepared according to the procedure described in Example 1, but using 4-hydroxybenzaldehyde.

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#### EXAMPLE 3

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3-(2-(1-Phenylmethoxycarbonyl-5-phenylmethoxy)indolyl)methoxybenzoic acid

The title compound was prepared according to the procedure described in Example 1, but using 3-hydroxybenzaldehyde.

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EXAMPLE 4

Benzyl (1-(2-(2-(1-oxo-2,2,2-trifluoroethyl)phenoxy)methyl-5-phenylmethoxy)indolyl)formate

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Step 1: Benzyl (1-(2-(2-(1-hydroxy-2,2,2-trifluoroethyl)phenoxy)methyl-5-phenylmethoxy)indolyl)-formate

A solution of 0.4 g (0.8 mmol) of the aldehyde, prepared in step 1 of Example 1, in 4 mL of THF was cooled to 0°C. To this were added 0.24 mL (1.6 mmol) of trifluoromethyl trimethylsilane and 5 mg of tetrabutylammonium fluoride trihydrate. The reaction was stirred for 2.5 hours at 0°C, and additional 0.2 mL (1.3 mmol) of trifluoromethyl trimethylsilane and 5 mg of tetrabutylammonium fluoride trihydrate were added. After stirred at 0°C for 2 hours, the reaction was worked up with aqueous ammonium chloride and ethyl acetate. Silica gel chromatographic purification using 4:1 hexane-ethyl acetate afforded corresponding TMS ether. Treatment of TMS ether with 1.3 mL of 1N HCl solution at room temperature, aqueous workup using brine and ethyl acetate and chromatographic purification using 3:1 hexane-ethyl acetate gave 230 mg of the titled compound.

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Step 2:

To a solution of 150 mg (0.27 mmol) of trifluoroethanol, prepared in step 1, in 5.5 mL of dichloromethane was added 255 mg (0.6 mmol) of the Dess-Martin's periodinate. The mixture was stirred at room temperature for 1 hour, and then partitioned between aqueous NaHCO<sub>3</sub> and ethyl acetate. The organic phase was washed once with aqueous NaHCO<sub>3</sub> and purified with chromatography using 3:1 hexane-ethyl acetate to yield 150 mg of the titled compound.

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EXAMPLE 53-(2-(1-Benzyl-5-benzyloxy)indolecarboxamido)benzoic acid5     Step 1: Ethyl 2-(1-benzyl-5-benzyloxy)indolecarboxylate

To a solution of 1 g (3.4 mmol) of ethyl 5-benzyloxyindole-2-carboxylate in 12 ml of DMF, sodium hydride (0.163g, 60% oil dispersion, 4.07 mmol) was added at room temperature. The reaction was stirred for 30 minutes. Benzyl bromide (0.44 mL, 3.73  
10     mmol) was added at this time and the reaction stirred for another hour. On completion of the reaction (monitored by TLC = 0.5 Rf in 3:1 Hexane:Ethyl acetate) it was quenched with water, extracted with ethyl acetate (3X). Organic layers were dried over magnesium sulfate, concentrated and used for the next step.

15     Step 2: 2-(1-Benzyl-5-benzyloxy)indolecarboxylic acid

The ester (3.4 mmol), prepared in step 2, was dissolved in THF (20 mL), methanol (20 mL) and then 1N NaOH (15 mL) was added. The reaction mixture was stirred at room temperature over night at which time it was concentrated, diluted with water, acidified to pH  
20     5 with 10% HCl and extracted with ethyl acetate (3X), the organic extracts were dried over magnesium sulfate and concentrated to give the indole acid ( 1.14 g, 94.2 %, TLC = 0.5 Rf in 1:1 Hexane:Ethyl acetate with 1% acetic acid).

Step 3: Ethyl 3-(2-(1-benzyl-5-benzyloxy)indolecarboxamido)benzoate

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The acid (0.54 g, 1.5 mmol) of step 2, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (0.32 g, 1.66 mmol), 4-dimethylaminopyridine (DMAP) (0.018 g, 0.15 mmol) and ethyl 3-aminobenzoate (0.27 g, 1.66 mmol) were stirred in tetrahydrofuran (9 mL) at room temperature overnight. The next day the reaction was diluted with ethyl  
30     acetate and water, extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using 3:1 hexane:ethyl acetate to give pure amide (0.578 g, 76%, TLC = 0.4 Rf in 3:1 Hexane:Ethyl acetate).



Step 4:

The ester (0.578 g, 1.15 mmol), prepared in step 3, was dissolved in THF (13.6 mL), methanol (13.6 mL) and then 1N NaOH (9.6 mL) was added. The reaction mixture was stirred at room temperature overnight at which time it was concentrated, diluted with water, acidified to pH 5 with 10% HCl and extracted with ethyl acetate (3X), the organic extracts were dried over magnesium sulfate and concentrated to give the titled compound (0.437 g, 80 %, TLC = 0.5 Rf in 3:1 hexane:ethyl acetate with 1 % acetic acid).

The Examples 6, 7, 8, 9, 10 and 11 in Table I were prepared by the procedures of Example 5 using suitable amines and alkyl halides.

EXAMPLE 12

3-(2-(3-(2,4-bis(1,1-dimethylpropyl)phenoxy)acetyl)-5-methoxy-1-methyl)indolyl) methylthioacetamido-4-methoxybenzoic acid

Step 1: 2-(5-Methoxy)indolylmethanol

Ethyl 5-methoxy-2-indolcarboxylate (30 g, 102 mmol) is dissolved in 250 mL of THF and cooled to 0° C and Lithium Aluminum Hydride (LAH) (255 mL of a 1.0 M solution in THF) is added via addition funnel over 40 minutes. The reaction was stirred a further 2 hours at 0° C and then worked up by the addition of 4N NaOH (190 mL). The resulting salts are filtered and washed with ethyl acetate (3X400 mL), the filtrates are combined and dried over MgSO<sub>4</sub> and concentrated to yield 24.8 g of alcohol, which was used for the next reaction directly.

Step 2: 2-(5-methoxy)indolylmethoxy-tert-butyldimethylsilane

The crude indole alcohol prepared in step 1 (6.2 g, 32.6 mmol) was dissolved in DMF (10.5 mL). To this solution was added imidazole (5.5g, 81.5 mmol) and t-butyldimethylsilyl chloride (5.4g, 35.8 mmol). The mixture was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate (3X). Organic layers were dried over magnesium sulfate and concentrated. The crude material was purified on a silica gel column using 19:1 hexane:ethyl acetate to give pure product (9.5g, 31 mmol, 94 % yield, TLC: 0.8 Rf in toluene:ethyl acetate 2:1)

Step 3: 3-(2-tert-butyldimethylsilyloxymethyl-5-methoxy)indolyl (2,4-bis(1,1-dimethoxypropyl)phenoxy)methyl ketone

2.32 g (7.95 mmol) of 2,4-Bis-tert-amylphenoxyacetic acid was dissolved in dichloromethane (21 mL), oxalyl chloride (1.4 mL 16.1 mmol) was added, followed by dimethyl formamide (0.5 mL) at room temperature. After one hour the reaction is concentrated and azeotroped with toluene and left on the high vacuum for two hours.

In another reaction vessel, a solution of the silyl protected indole, prepared in step 2, (2 g, 6.56 mmol) in ether (20 mL) was added dropwise to ethyl magnesium bromide (2.4 mL of a 3M solution in ether, 7.2 mmol) in ether (10 mL), the latter maintained at -78°C. The reaction was stirred at -60°C for 2 hr. To this reaction solution, the above prepared acid chloride in ether (4 mL) was added slowly. The reaction was maintained between -50°C and -60°C for another 2 hrs. The reaction was then quenched with saturated sodium bicarbonate. Extracted with ethyl acetate (3X). Organic layers were dried over magnesium sulfate and concentrated. The crude material was purified on a silica gel column using 19:1 Hexane:Ethyl acetate to give pure product (2.36 g, 50%, TLC: 0.15 Rf in hexane:ethyl acetate 19:1).

Step 4: 3-(2-tert-butyldimethylsilyloxymethyl-5-methoxy-1-methyl)indolyl (2,4-bis(1,1-dimethoxypropyl)phenoxy)methyl ketone

To the ketone (1.97g, 3.4 mmol) of in step 3 in 12 mL of DMF, sodium hydride (0.163g, 60% oil dispersion, 4.07 mmol) was added at room temperature. The reaction was

stirred for 30 minutes. Methyl iodide (0.23 mL, 3.73 mmol) was added at this time and the reaction stirred for another hour. On completion of the reaction (monitored by TLC) it was quenched with water, extracted with ethyl acetate (3X). Organic layers were dried over magnesium sulfate, concentrated and the crude product was used for the next step.

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Step 5: 3-(2-Hydroxymethyl-5-methoxy-1-methyl)indolyl (bis-2,4-(1,1-dimethylpropyl)phenoxy)methyl ketone

A mixture of N-methyl indole, prepared in step 4, (2.01 g, 3.4 mmol) and tetra-butyl ammoniumfluoride (TBAF) (8.5 mL of a 1M solution in THF, 8.5 mmol) in THF (17.9 mL) were stirred at room temperature for one hour. At this time the reaction was diluted with ethyl acetate and water, extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using hexane:ethyl acetate 2:1 to yield pure alcohol (0.82 g, 60 %, TLC: 0.3 Rf in 2:1 hexane:ethyl acetate).

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Step 6: Methyl 3-(2-(3-(2,4-bis(1,1-dimethylpropyl)phenoxy)acetyl-5-methoxy-1-methylindolyl)methylthioacetamido)-4-methoxybenzoate

The indole alcohol, prepared in step 5, (0.20 g, 0.43 mmol) was dissolved in dichloromethane (0.7 mL) and treated with triethylamine (0.1 mL, 0.64 mmol) and cooled to 0° C at which time mesyl chloride (0.04 mL 0.52 mmol) was added over 5 minutes, followed by addition of two drops of DMF. The reaction was stirred for a further 2 hour at 0C, it was then concentrated and used directly for the next reaction.

The above prepared mesylate was dissolved in DMF (0.8 mL). The solution was degassed by bubbling nitrogen through for ten min. Cesium carbonate (0.25 g, 1.29 mmol) was added and then thiol (0.11 g, 0.43 mmol), prepared in Intermediate 1, was added. The mixture was stirred overnight, then poured into saturated ammonium chloride and extracted with ethyl acetate (3X), dried, concentrated. The crude material was purified on a silica gel column using hexane:ethyl = 2:1 acetate to give pure product (0.12 g, 40%, TLC: 0.3 Rf in hexane:ethyl acetate 1:1).

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Step 7:

The ester, prepared in step 6, (0.12 g, 0.17 mmol) was dissolved in THF (1.0 mL), methanol (1.0 mL) and then 1N NaOH (0.4 mL) was added. The reaction mixture was stirred at room temperature overnight at which time it was concentrated, diluted with water, acidified to pH 5 with 10% HCl and extracted with ethyl acetate (3X), the organic extracts  
5 were dried over magnesium sulfate and concentrated to give the titled compound (85 mg, 72 %, TLC = 0.3 Rf in 1:1 Hexane:Ethyl acetate with 1% acetic acid).

EXAMPLES 13, 14, 15 and 16 in Table I were prepared by the procedures of Example 12  
10 using Ethyl 2-(5-benzyloxy)indolecarboxylate, acetyl chlorides and suitable alkyl halides.

#### EXAMPLE 17

15 3-(2-(-5-benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indolinyl)  
methylthioacetamidobenzoic acid

#### Step 1: 2-(5-Benzyloxy)indolinylmethanol

Ethyl 5-benzyloxy-2-indolecarboxylate (30 g, 102 mmol) was dissolved in 250 mL of THF  
20 and cooled to 0° C, to which Lithium Aluminum Hydride (LAH) (255 mL of a 1.0 M solution in THF) was added via addition funnel over 40 minutes. The reaction was stirred a for 2 hours at 0° C and then worked up by the addition of 4N NaOH (190 mL). The resulting salts were filtered and washed with ethyl acetate (3X400 mL), the filtrates were combined, dried over MgSO<sub>4</sub> and concentrated to yield 24.8 g. This crude material was then dissolved  
25 in glacial acetic acid (260 mL) and the resulting yellow solution was cooled to 15 C, sodium cyanoborohydride (18.5 g, 294 mmol) was added portionwise over 10 minutes, and the resulting mixture was stirred for 3 hours. The reaction was quenched by pouring slowly into 1.5 liters of nearly saturated NaHCO<sub>3</sub>, extracted with ethyl acetate (3X), dried over MgSO<sub>4</sub> and concentrated to yield a orange solid (29.6 g).

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#### Step 2: tert-Butyl 1-(5-benzyloxy-2-hydroxymethyl)indolinylformate

25 g (85 mmol) of crude alcohol, prepared in step 1, and 4-dimethylamino pyridine (DMAP) (1.19 g, 9.78 mmol) were dissolved in dichloromethane (180 mL). The solution was cooled to 0° C and then triethylamine (13.6 mL, 98 mmol) was added to it. After 10 minutes of stirring a solution of di-tert-butyl dicarbonate (21.3 mL, 98mmol) dissolved in dichloromethane (20 mL) was added via syringe pump over 2 hours. After 1 hour of stirring the reaction was quenched by the addition of 1/2 saturated NH<sub>4</sub>Cl solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X), dried over MgSO<sub>4</sub> and concentrated to yield 36.3 g of a yellow oil, which was purified by column chromatography using a hexane:ethyl acetate gradient of 9:1 to 4:1 to 1:1 to deliver the product (15.25 g, 44%).

Step 3: Ethyl 2-(5-benzyloxy-1-tert-butoxycarbonyl)indolinylmethylthioacetate

The carbamate, prepared in step 2, (15.25 g, 43 mmol) was dissolved in dichloromethane (180 mL) and treated with triethylamine (9.0 mL, 64.4 mmol). The solution was cooled to -10° C at which time mesyl chloride (4.3 mL, 56 mmol) was added over 5 minutes. The reaction was stirred for a further 2 hour at -10°C, it was then concentrated and used directly for the next displacement reaction.

The above prepared mesylate was dissolved in DMF (85 mL, degassing the solvent is strongly recommended) cesium carbonate (35 g, 107.3 mmol) was added and then ethyl thioacetate (4.70 mL, 42.9 mmol) was added. The mixture was stirred for 1 day, then poured into 1/2 saturated ammonium chloride and extracted with ethyl acetate (3X), dried, concentrated and chromatographed (hexane:ethyl acetate gradient 10:1 to 4:1) to yield 8.55 g of a yellow oily product.

Step 4: 2-(5-Benzyloxy-1-tert-butoxycarbonyl)indolinylmethylthioacetic acid

To a solution of the indoline ester, prepared in step 3, (5g, 11 mmol) in 1M potassium hydroxide in methanol (100 mL), water (10 mL) was added. The reaction was stirred at room temperature for two hours at which time it was diluted with water, acidified to pH 5 with 10% HCl and extracted with ethyl acetate (3X), the organic extracts were dried over magnesium sulfate and concentrated to give the indoline acid ( 4.5g, 95.5%, TLC = 0.5

Rf in 2:1 hexane:ethyl acetate with 1% acetic acid). The crude material was used for the next step directly.

5 Step 5: Ethyl 3-(2-(5-benzyloxy-1-tert-butoxycarbonyl)indoliny)methylthioacetamidobenzoate

10 The acid (3g, 7 mmol), prepared in step 4, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.6g, 8.4 mmol), 4-dimethylaminopyridine (0.85g, 7 mmol) and ethyl 3-aminobenzoate (1.27 g, 7.7 mmol) were stirred in tetrahydrofuran (43 mL) at room temperature overnight. On next day the reaction was diluted with ethyl acetate and water, extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using 3:1 hexane:ethyl acetate to give the product (3.4g, 85%, TLC = 0.3 Rf in 3:1 hexane:ethyl acetate).

15 Step 6: Ethyl 3-(2-(5-benzyloxy)indoliny)methylthioacetamidobenzoate

20 To the indoline (3.4g, 5.9 mmol) of step 5, trifluoroacetic acid (24 mL) was added and the reaction stirred for 1 hour at 0°C. The reaction was quenched by the addition of water and the TFA neutralized by the addition of sodium bicarbonate, the aqueous layer was extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using 2:1 hexane:ethyl acetate to yield product (2.7 g, 96%, TLC = 0.3 Rf in 2:1 hexane:ethyl acetate).

25 Step 7: Ethyl 3-(2-(5-benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indoliny)methylthioacetamidobenzoate

30 The 2,4-bis(1,1-dimethylpropyl)phenoxyacetic acid (0.228 g, 0.78 mmol) was dissolved in dichloromethane (2 mL), to which oxalyl chloride (0.14 mL 1.6 mmol) was added followed by dimethyl formamide (0.1 mL) at room temperature. After one hour the reaction is concentrated and azeotroped with toluene and left on the high vacuum for two hours. The indoline ester (0.308 g, 0.65 mmol), prepared in step 6, and 4-dimethylaminopyridine (0.008 g, 0.066 mmol) were dissolved in dichloromethane (1.2 mL)

and then the above prepared acid chloride in dichloromethane (0.5mL) was added followed by the addition of triethylamine (0.28mL, 1.95 mmol). The reaction was stirred at room temperature overnight, and then diluted with ethyl acetate and water, extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was  
5 purified on silica gel using 2:1 hexane:ethyl acetate to yield product (0.291 g, 60 %, TLC = 0.4 Rf in 2:1 hexane:ethyl acetate).

Step 8:

10 The ester (0.231 g, 0.31 mmol) of step 7 was dissolved in THF (4.3 mL), methanol (4.3 mL) and then 1N NaOH (3.2 mL) was added. The reaction mixture was stirred at room temperature overnight at which time it was concentrated, diluted with water, acidified to pH  
5 with 10% HCl and extracted with ethyl acetate (3X), the organic extracts were dried over magnesium sulfate and concentrated to give the titled product ( 0.207 g, 93.2 %, TLC = 0.3  
15 Rf in 2:1 hexane:ethyl acetate with 1.5 % acetic acid).

EXAMPLE 18

20 3-(2-(-5-Benzoyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indolinyl)  
methylthioacetamido-4-methylbenzoic acid

Step 1: Ethyl 2-(5-benzyloxy)indolinylmethylthioacetate

25 The N-tert-butoxycarbonyl indoline (3.0 g, 6.6 mmol), prepared in step 3 of Example 17, was added to a flask and cooled to 0°C. To this reaction mixture trifluoroacetic acid was added (35 mL) and the reaction was stirred for 1 hour at 0°C and then 1 hour at rt. The reaction was quenched by the addition of water, and the TFA was neutralized by the addition of solid sodium bicarbonate, the aqueous layer was extracted with ethyl acetate (4X) and  
30 dried over magnesium sulfate and concentrated to an orange oil (1.85 g, 79%) that was used directly for the next step.

Step 2: Ethyl 2-(5-benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)-indolinylmethylthioacetate

2,4-Bis(1,1-dimethyl)propyl)phenoxyacetic acid (2.0g, 6.8 mmol), dichloromethane  
5 (15 mL), oxalyl chloride (1.2 mL, 13.6 mmol), dimethylformamide (0.1 mL) were stirred at  
0° C for 45 minutes at which time the reaction is concentrated and azeotroped with toluene  
(1X) and concentrated on the high vac for 2 hours before use. The indoline ester (1.85g, 5.2  
mmol), prepared in step1, and 4-dimethylaminopyridine (0.08 g) were dissolved in  
dichloromethane (15 mL) and then the above generated acid chloride in dichloromethane (5  
10 mL) was added followed by the addition of triethylamine (0.95 mL, 6.8 mmol). The reaction  
was stirred 16 hours at rt, worked up and concentrated (4.0 g, orange oil), chromatographed  
using a 9:1 to 6:1 gradient of hexane:ethyl acetate to yield the product (2.5g, 75%) that was  
used for the next step without further purification.

15 Step 3: 2-(5-Benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indolinylmethylthioacetic acid

The ester (2.5 g, 3.9 mmol), prepared in step 2, was dissolved in THF (20 mL),  
methanol (6 mL) and then 1N sodium hydroxide (12 mL) was added. The resulting mixture  
20 was stirred 24 hours at which time it was concentrated, diluted with water, acidified to pH 4  
with concentrated HCl and extracted with ethyl acetate (4X), the organic extracts were dried  
over magnesium sulfate, concentrated, and purified via chromatography (3:1 hexane:ethyl  
acetate with 1% acetic acid) to yield 1.17 g ( 50%) of the product as white solid.

25 Step 4: Methyl 3-(2-(5-benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indolinylmethylthioacetamido-4-methylbenzoate

The acid (0.20 g, 0.33 mmol), prepared in step 3, EDCI (0.08 g, 0.43 mmol),  
DMAP (4 mg, 0.03 mmol) and methyl 3-amino-4-hydroxy benzoate (0.06 g, 0.33 mmol)  
30 were dissolved in THF (3 mL) and refluxed 16 hours. Aqueous workup with ammonium  
chloride and ethyl acetate and purification via silica gel chromatography (hexane:ethyl acetate  
3:1) yielded 0.13 g (52%) of the product as a white solid.



Step 5:

The titled compound was prepared from ester, prepared in step 4, according to the procedure described in step 3.

5

EXAMPLES 17 to 36 in Table 2 were prepared according to the procedures described in either Example 17 or Example 18.

10

EXAMPLE 372-(5-Benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methylthioacetic acid5     Step 1: 2-(5-Benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methanol

A 1-L oven-dried round bottom flask fitted with a magnetic stirring bar and equalizing dropping funnel was charged with 17.0 g ( 59 mmol) of 3,5-bis(trifluoromethyl)phenoxyacetic aci, DMF (5 drops) and anhydrous  $\text{CH}_2\text{Cl}_2$  (300 mL).  
10     Oxalyl chloride (23 mL, 263 mmol) was added dropwise over 10 min. After stirring for 2.5 h at room temperature solvent, excess oxalyl chloride were removed in vacuo to afford acid chloride as a white solid. This was used immediately in the next reaction.

A 1-L oven-dried round bottom flask fitted with a magnetic stirring bar and equalizing dropping funnel was charged with 15.3 g (60 mmol) of 2-(5-Benzyloxy)indolinylmethanol, prepared in step1 of Example 17, DMAP (0.73 g, 6 mmol)  
15     and anhydrous  $\text{CH}_2\text{Cl}_2$  (300 mL). After cooling to 0°C, a solution of above prepared acid chloride (59 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (100 mL) was added dropwise, followed by  $\text{NEt}_3$  (9 mL, 64.7 mmol). After stirring for 1 h at 0°C the reaction mixture was washed with  
20     saturated  $\text{NaHCO}_3$  solution (100 mL), 1 N HCl solution (100 mL) and  $\text{H}_2\text{O}$  (100 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuo. Purification by column chromatography in silica gel using 25-40% AcOEt in hexane afforded product as a light yellow solid. Yield 22.0 g (71 %).

25     Step 2: Ethyl 2-(5-benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methylthioacetate

A 500-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with alcohol (19.0 g, 36.15 mmol), prepared in step 1, anhydrous  $\text{CH}_2\text{Cl}_2$  (300 mL),  
30     and  $\text{NEt}_3$  (7.5 mL, 54.23 mmol).  $\text{MsCl}$  was added dropwise over 2 min and the reaction mixture was stirred at room temperature for 10 min. The solution was diluted with  $\text{CH}_2\text{Cl}_2$  (500 mL) and washed with 1N HCl solution (100 mL) and saturated  $\text{NaHCO}_3$  solution (100

mL). The  $\text{CH}_2\text{Cl}_2$  solution was dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed and the mesylate was used in the next step without further purification.

5 A 500-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with ethyl thioacetate (4.2 mL, 38.5 mmol), and anhydrous THF (75 mL). After cooling in a dry ice/acetone bath  $\text{NaN}(\text{SiMe}_3)_2$  (1 M solution in THF, 50 mL, 50 mmol) was added. After 15 min a solution of above prepared mesylate (21 g, 35 mmol) in anhydrous THF (60 mL) was added. After 15 min the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 100 min the reaction was heated at reflux for 4 h. The solution was allowed to cool to room temperature. It was diluted with  $\text{CHCl}_3$  (500 mL), washed with saturated  $\text{Na}_2\text{CO}_3$  solution (200 mL) and 1N HCl solution (200 mL). The organic solution was dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuo. The crude material was purified by column chromatography on silica gel using 15% AcOEt in hexane to afford 13.8 g (63%) of product.

15 Step 3:

A 250-mL round bottom flask fitted with a magnetic stirring bar was charged with ester (12.45 g, 19.8 mmol), prepared in step 2, THF (100 mL), MeOH (33 mL) and  $\text{H}_2\text{O}$  (33 mL).  $\text{LiOH}\cdot\text{H}_2\text{O}$  (1.08 g, 25.7 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The solvents were removed in vacuo. The residue was taken into 1N HCl solution (200 mL) and extracted with AcOEt (2 x 400 mL). The combined extracts were washed with 1 N HCl solution (100 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuo to afford the titled compound. Yield 11.9 g (100%).

25

EXAMPLE 38

5-(2-(5-Benzoyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indolinyl)methylthioacetamido)benzene-1,3-dicarboxylic acid

Step 1: 5-(2-(5-Benzoyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indolinyl)methylthioacetamido)benzene-1,3-dicarboxylate

10 A 100-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with acid (1.2 g, 2 mmol), prepared in step 3 of Example 37, anhydrous THF (40 mL), EDCI (0.544 g, 2.8 mmol), DMAP (0.024 g, 0.2 mmol), and 5-amino-1,3-benzenedicarboxylic acid (0.46 g, 2.2 mmol). The reaction mixture was heated at reflux until no change was detected by TLC. The solvent was removed in vacuo. The residue was  
15 dissolved in CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with 1 N HCl solution (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was removed in vacuo. The crude material was purified by column chromatography on silica gel using 1-2% MeOH in CHCl<sub>3</sub> to afford 1.2 g (77%) of product.

Step 2:

20 A 25-mL round bottom flask fitted with a magnetic stirring bar was charged with ester (0.6 g, 0.76 mmol), prepared in step 1, THF (7.5 mL), MeOH (2.5 mL) and H<sub>2</sub>O (2.5 mL). LiOH·H<sub>2</sub>O (0.084 g, 2 mmol) was added, and the reaction mixture was stirred at room temperature for 6 h. The solvents were removed in vacuo. The residue was taken into 1N  
25 HCl solution (10 mL) and extracted with AcOEt (2 x 50 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered and removed in vacuo. The crude material was purified by column chromatography on silica gel (eluant: 5% MeOH in CHCl<sub>3</sub> + 0.5-0.7% AcOH) to yield 0.28 g (46%) of the titled compound.

30

EXAMPLES 39, 40, 43 in Table 3 were prepared according to the procedurs described in either Example 38.

EXAMPLE 41

5     5-(2-(-5-Benzoyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methylthioacetamido)-3-hydroxymethylbenzoic acid

Step 1: Methyl 5-(2-(-5-benzoyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methylthioacetamido)-3-tert-butyl dimethylsilyloxymethylbenzoate

10

This compound was prepared according to the procedure described in step 1 of Example 38.

Step 2: Methyl 5-(2-(-5-benzoyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methylthioacetamido)-3-hydroxymethylbenzoate

15

A 25-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with silyl protected ester (1.32 g, 1.5 mmol), prepared in step 1, anhydrous THF (10 mL), and TBAF (1 M solution in THF, 2.5 mol equiv.). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed in vacuo. The oily residue was purified by column chromatography on silica gel using 0-30% AcOEt in CH<sub>2</sub>Cl<sub>2</sub> to afford 0.94 g (92%) of desired product.

20

Step 3:

25

The titled compound was prepared according to the procedure described in step 2 of Example 38.

30     EXAMPLE 42 in table 3 was prepared according to the procedures described in Example 41.

EXAMPLE 44

5-(2-(-5-Hydroxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methylthioacetamido)benzene-1,3-dicarboxylic acid

5

Step 1: 2-(5-Hydroxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methanol

A 500-mL Parr Hydrogenation bottle was charged with 2-(5-Benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methanol (10 g, 19.1 mmol), prepared in step 1  
10 of Example 37, 5% Pd on carbon (1.0 g), AcOEt (150 mL) and MeOH (100 mL) and subsequently hydrogenated at 50 psi for 18 h. The reaction mixture was filtered through Celite and concentrated in vacuo to afford crude product. This was used in the next step reaction without further purification.

15 Step 2: 2-(5-(4-Methoxy)benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methanol

A 1-L oven-dried round bottom flask fitted with a magnetic stirring bar and reflux condenser was charged with alcohol (8.56 g, 19.7 mmol), prepared in step 1, 200 mesh  
20 K<sub>2</sub>CO<sub>3</sub> (6.53 g, 47.2 mmol), KI (3.91 g, 23.6 mmol) and finally the p-methoxy benzyl chloride (3.2 mL, 23.6 mmol) in 450 mL of anhydrous acetonitrile. The reaction mixture was heated at reflux for 4 h. The reaction mixture was partitioned between AcOEt (500 mL) and H<sub>2</sub>O (200 mL). The aqueous layer was extracted with AcOEt (3 x 500 mL). The combined AcOEt extracts were washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered.  
25 The solvents were removed in vacuo. Purification of the residue by column chromatography on silica gel (eluant: 40% AcOEt in hexane) afforded desired product. Yield 8.7 g (83%).

Step 3: Methyl 5-(2-(-5-(4-methoxy)benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indoliny)methylthioacetamido)benzene-1,3-dicarboxylate

30

A 100-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with alcohol (3.2 g, 5.77 mmol), prepared in step 2, and anhydrous CH<sub>2</sub>Cl<sub>2</sub> (44 mL).

The reaction mixture was cooled to 0°C and added anhydrous Et<sub>3</sub>N (1.2 mL, 8.61 mmol) followed by MsCl (0.53 mL, 6.84 mmol). The reaction mixture was stirred at 0°C for 5 min. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and H<sub>2</sub>O (50 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with 1 N HCl solution (100 mL), saturated NaHCO<sub>3</sub> solution (100 mL), H<sub>2</sub>O (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were removed in vacuo to afford mesylate. This was used in the next step reaction without further purification.

A 100-mL oven-dried round bottom flask fitted with a magnetic stirring bar and reflux condenser was charged with above prepared mesylate (3.60 g, 5.70 mmol), anhydrous Cs<sub>2</sub>CO<sub>3</sub> (5.19 g, 15.9 mmol) and anhydrous DMF (20 mL). The reaction solution was passed through N<sub>2</sub> for 15 min. Methyl 5-thioacetamido-1,3-benzenedicarboxylate, prepared in Intermediate 2, was added in one portion and the reaction mixture was heated at 50 °C for 18 h. The reaction mixture was partitioned between AcOEt (500 mL) and H<sub>2</sub>O (200 mL). The aqueous layer was extracted with AcOEt (3 x 100 mL). The combined AcOEt extracts were washed with saturated Na<sub>2</sub>CO<sub>3</sub> solution (100 mL), H<sub>2</sub>O (100 mL), brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were removed in vacuo. Purification of the residue by column chromatography on silica gel (eluant: 5% AcOEt in CH<sub>2</sub>Cl<sub>2</sub>) afforded product. Yield 2.5 g (53%).

Step 4: Methyl 5-(2-(-5-Hydroxy-1-(3,5-bis(trifluoromethyl)phenoxy)acetyl)indoliny)methylthioacetamido)benzene-1,3-dicarboxylate

A 100-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with ester (2.60 g, 3.17 mmol), prepared in step 3, and anhydrous CH<sub>2</sub>Cl<sub>2</sub> (30 mL). To the reaction mixture was added TFA (25 mL) in several portions over 1 min. The reaction mixture was poured onto 500 mL saturated NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with saturated Na<sub>2</sub>CO<sub>3</sub> solution (200 mL), H<sub>2</sub>O (200 mL), brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were removed in vacuo. Purification of the residue by column chromatography on silica gel (eluant: 12.5% - 20% AcOEt in CH<sub>2</sub>Cl<sub>2</sub>) afforded the product. Yield 1.5 g (68%).

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Step 5:

A 25-mL round bottom flask fitted with a magnetic stirring bar was charged with ester (270 mg, 0.40 mmol), prepared in step 4, LiOH hydrate (3.3 equiv.), THF (3.6 mL),  
5 MeOH (1.2 mL) and H<sub>2</sub>O (1.2 mL). The reaction mixture was heterogeneous with white solid suspended in the solution. After stirring for 4 h, more solvents were added in 3 : 1 : 1 = THF : MeOH : H<sub>2</sub>O to make a clear solution. The reaction mixture was stirred at room temperature for 18 h and monitored by TLC. The reaction mixture was acidified with 1 N HCl solution to pH = 2 or with acetic acid to pH = 4 and then partitioned between AcOEt  
10 (20 mL) and H<sub>2</sub>O (20 mL). The aqueous layer was extracted with AcOEt (3 x 20 mL). The combined AcOEt extracts were washed with H<sub>2</sub>O (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were removed in vacuo. Purification of the residue by column chromatography on silica gel followed by recrystallization from acetone / hexane afforded  
15 130 mg of the titled compound (50%).

EXAMPLE 45

5-(2-(5-(3,5-Dibromo)benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)indolinyl)  
20 methylthioacetamido)benzene-1,3-dicarboxylic acid

Step1: Methyl 5-(2-(5-(3,5-Dibromo)benzyloxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl)  
indolinyl)methylthioacetamido)benzene-1,3-dicarboxylate

25 A 25-mL oven-dried round bottom flask fitted with a magnetic stirring bar and reflux condenser was charged with methyl 5-(2-(5-Hydroxy-1-(3,5-bis(trifluoromethyl)phenoxyacetyl) indolinyl)methylthioacetamido)benzene-1,3-dicarboxylate (0.19 g, 0.27 mmol), prepared in step 4 of Example 4, 200 mesh K<sub>2</sub>CO<sub>3</sub> (2.4 equiv.) and 3,5-dibromobenzyl bromide (1.2 equiv.) in 7.5 mL of anhydrous acetonitrile. The reaction  
30 mixture was heated at 70°C for 2 h. The reaction mixture was partitioned between AcOEt (30 mL) and H<sub>2</sub>O (20 mL). The aqueous layer was extracted with AcOEt (3 x 30 mL). The combined AcOEt extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered.

The solvents were removed in vacuo. Purification of the residue by column chromatography on silica gel using 15 % EtOAc in dichloromethane afforded 0.20 g of the product (77%).

Step 2:

5

The titled compound was prepared from the ester, prepared in step 1, according to the procedure described in step 5 of Example 44.

10 EXAMPLES 46 to 50 in table 4 were prepared according to the procedures described in Example 44, but using corresponding alkylating reagent.

EXAMPLE 51

15

Methyl 3-(2-(5-benzyloxy-1-(4-benzylbenzoyl)indoliny)methylthioacetamido)benzoate

4-Benzylbenzoic acid (0.19g, 0.91 mmol) was dissolved in dichloromethane (2.3 ml), next oxalyl chloride (0.16 mL, 1.82 mmol) was added followed by dimethylformamide (0.5 mL) at room temperature. After one hour the reaction was concentrated and azeotroped with toluene and left on high vacuum for two hours.

20 Ethyl 3-(2-(5-benzyloxy)indoliny)methylthioacetamidobenzoate (0.308 g, 0.65 mmol), prepared in step 6 of Example 17, and 4-dimethylaminopyridine (8 mg, 0.066 mmol) were dissolved in dichloromethane (1.2 mL) and then the above prepared acid chloride in dichloromethane (0.5 mL) was added followed by the addition of triethylamine (0.28 mL, 1.95 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with ethyl acetate and water, extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using 2:1 hexane:ethyl acetate to yield 0.354 g of the titled product (81.7%, TLC = 0.4 R<sub>f</sub> in 2:1 hexane:ethyl acetate).

25

30



EXAMPLE 523-(2-(5-Benzoyloxy-1-(4-benzylbenzoyl)indolinyl)methylthioacetamido)benzoic acid

5           The ester (0.354 g, 0.53 mmol), prepared in Example 51, was dissolved in THF (5.6 mL), methanol (5.6 mL) and then 1N NaOH (4.2 mL) was added. The reaction mixture was stirred at room temperature overnight at which time it was concentrated, diluted with water, acidified to pH 5 with 10% HCl and extracted with ethyl acetate (3X). The organic extracts  
10       %, TLC = 0.3 R<sub>f</sub> in 2:1 hexane:ethyl acetate with 1.5 % acetic acid).

EXAMPLES 53 to 58 in Table 5 were prepared according to the procedures described in Example 51 and 52.

15

EXAMPLE 59

3-(2-(5-Benzoyloxy-1-(2-naphthoxyacetyl)indolinyl)methylthioacetamido)-4-methoxybenzoic acid  
20       acid

Step 1: Methyl 3-(2-(5-benzoyloxyindolinyl)methylthioacetamido)-4-methoxybenzoate

25       This compound was prepared according to the procedures described in step 6 of Example 17, but with methyl 4-methoxybenzoate.

Step 2: Methyl 3-(2-(5-benzoyloxy-1-(2-naphthoxyacetyl)indolinyl)methylthioacetamido)-4-methoxybenzoate

30       The indole ester (0.22 g, 0.45 mmol), prepared in step 1, 2-naphthoxyacetic acid (0.11 g, 0.53 mmol), EDCI (0.10 g, 0.53 mmol) and DMAP (5 mg, 0.04 mmol) were weighed into a flask that was equipped with a condenser, flushed with nitrogen, and then

tetrahydrofuran (5 mL) was added and the reaction was brought to reflux for 18 hours; the reaction was diluted with 1/2 saturated ammonium chloride and ethyl acetate, extracted 3X with ethyl acetate, dried over magnesium sulfate, concentrated to yield (0.30 g, 100% crude) a white solid that was used without purification.

5

Step 3:

The ester (0.12 g, 0.20 mmol), prepared in step 2, was dissolved in THF/ methanol and then 1N sodium hydroxide (0.8 mL) was added and the resulting mixture was stirred 16  
10 hours at RT and a further 5 hours at 49°C, workup yielded 0.12 g of a yellow solid that was purified via preparative TLC (1:1 hexane:ethyl acetate with 1% acetic acid) to yield 0.12 g of the titled product (95%).

15 EXAMPLES 60 to 63 in Table 5 were prepared according to the procedures described either in Example 59 or in Examples 51 and 52.

EXAMPLE 64

20

3-(2-(5-benzyloxy-1-tert-butoxycarbonyl)indoliny)methylsulfonylacetamidobenzoic acid

Step 1: Ethyl 3-(2-(5-benzyloxy-1-tert-butoxycarbonyl)indoliny)methylsulfonyl  
acetamidobenzoate

25

To a solution of Ethyl 3-(2-(5-benzyloxy-1-tert-butoxycarbonyl)indoliny)methyl  
lthioacetamidobenzoate (0.05g, 0.09 mmol), prepared in step 5 of Example 17, in  
dichloromethane (0.1 mL) at room temperature, m-chloroperbenzoic acid (0.06g of 60% m-  
cPBA, 0.21 mmol) was added and the reaction stirred overnight. Next day the reaction was  
30 quenched with an aqueous solution of sodium bicarbonate, extracted with ethyl acetate (3X),  
dried over magnesium sulfate and concentrated. The crude sulfone (0.52g, 98%, TLC = 0.3  
R<sub>f</sub> in 1:1 hexane:ethyl acetate) was used for the next reaction directly.



Step 2:

The titled compound was prepared according to the procedure described in step 3 of Example 59.

5

EXAMPLES 66 and 65 were prepared according to the procedures described in Example 18.

10 EXAMPLE 67

2-(2-(5-Benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indolinyl)methylthiobenzoic acid

15 Step 1: 5-Benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl-2-hydroxymethylindoline

The diisopropylethylamine (3.5 mL, 20.5 mmol), DMAP(0.25 g, 2.05 mmol) and the indoline alcohol (4.53 g, 17.7 mmol), prepared in step 1 of Example 17, were weighed into a flask which was flushed with nitrogen and cooled to 0 °C at which time a 0 °C solution of di-tert-amylphenoxyacetyl chloride (20.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added via cannula. The resulting solution was left to warm to room temperature overnight and then quenched by the addition of 1/2 saturated ammonium chloride and CH<sub>2</sub>Cl<sub>2</sub>, the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X), the combined layers were dried over magnesium sulfate and concentrated to yield (10.4 g) of a yellow foam that was purified via chromatography using a gradient (hexane:ethyl acetate 7:1 to 3:1 to 1:1) to yield 3.62 g of the product.

Step 2: 2-(5-Benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indolinylmethyl methylsulfonate

To a solution of alcohol (1.2 g, 2.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL), prepared in step 1, is added triethylamine (0.44 mL, 3.16 mmol). The solution is brought to -50°C and then mesyl chloride (0.23 mL, 2.93 mmol) is added. The mixture is stirred 2 h at -50°C,

quenched with saturated ammonium chloride and allowed to come to rt. The mixture is taken up in  $\text{CHCl}_3$  (50 mL), washed with saturated sodium bicarbonate (1 X 10 mL), brine (1 X 10 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated to afford the product (1.19 g, 86%).

5     Step 3: Methyl 2-(2-(-5-benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indoliny) methylthiobenzoate

To a solution of mesylate (0.54 g, 0.89 mmol), prepared in step 2, in degassed DMF (2 mL) is added  $\text{CsCO}_3$  (0.724 g, 2.22 mmol) and methyl thiosalicylate (0.134 mL, 0.98 mmol). The mixture is stirred 4 h, taken up in ethyl acetate (20 mL), washed with brine (3 X 3 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated. Chromatography (gradient, hexane:ethyl acetate 15:1 to 4:1) afforded 0.53 (86%) of the title compound as a yellow oil.

15     Step 4:

The titled compound was prepared according to the procedure described in step 3 of Example 59.

20     EXAMPLE 68 was prepared according to the procedures described in Example 67.

EXAMPLE 69

25     3-(N-(2-(-5-Benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indoliny) methylthioethyl)aminobenzoic acid

The titled product was prepared according to the procedures described in step 3 of Example 59, but using Intermediate 15.

30



EXAMPLE 70

3-N-Methyl-(2-(-5-Benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)phenoxyacetyl)indolinyloxy)-  
methylthioacetamido-4-methoxybenzoic acid

5

An oven-dried 100 mL, 3-neck round bottom flask, equipped with a stir bar and nitrogen inlet, was charged with methyl 3-(2-(-5-Benzyloxy-1-(2,4-bis(1,1-dimethyl)propyl)-phenoxyacetyl)indolinyloxy)-methylthioacetamido-4-methoxybenzoate (581 mg, 0.757 mmol), prepared in the synthesis of Example 20 using the procedures described in Example 18, and 10 mL of THF was added via syringe. To the resulting yellow solution was added NaH (60% suspension in mineral oil, 39 mg, 0.975 mmol). The reaction mixture was stirred at 25 °C for 1.5 h to afford a pale suspension. Methyl iodide (161 mg, 1.14 mmol) was added, and the reaction mixture was stirred at 25 °C for 2 days. After chilling to 0 °C, water was added (10 mL), followed by 50 mL of half saturated ammonium chloride, and 100 mL of EtOAc.

15 The layers were separated, and the aqueous phase was extracted once with EtOAc (50 mL). The combined organic phases were dried (sodium sulfate), filtered, and concentrated to afford 0.6 g of crude product as an orange oil. This material was dissolved in 15 mL of THF and 10 mL of methanol, and 7 mL of 1N NaOH solution was added, under nitrogen. After being stirred for 2 h at 25 °C, the reaction mixture was concentrated to dryness on the rotary, and 100 mL of 1N HCl, and 100 mL of EtOAc were added. The layers were separated, and the organic phase was dried (magnesium sulfate), filtered, and concentrated. The crude material obtained (0.565 g) was purified by column chromatography on silica gel (eluant: chloroform to 3% MeOH in chloroform) to afford the titled compound (0.415 g, 70% yield).

20

25

EXAMPLE 71 was prepared according to the procedures described in Example 70, but using allyl bromide.

30

EXAMPLE 72

3-(2-(5-benzyloxy-1-(2-(4-pyridinyl)ethyl)indoliny)l)methylthioacetamidobenzoic acid

5 Step 1: Ethyl 3-(2-(5-benzyloxy-1-(2-(4-pyridinyl)ethyl)indoliny)l)methylthioacetamidobenzoate

To a solution of ethyl 3-(2-(5-benzyloxy)indoliny)l)methylthioacetamidobenzoate (0.30 g, 0.63 mmol), prepared in step 6 of Example 17, in dichloromethane (3.0 mL) and acetic acid (2.0 mL), 4-vinylpyridine (0.08 mL, 0.75 mmol) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with half saturated sodium bicarbonate, extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using a gradient of 2:1 hexane:ethyl acetate to 100% ethyl acetate to yield 0.023 g of product (25 %, TLC = 0.7 R<sub>f</sub> in ethyl acetate).

Step 2:

The titled compound was prepared according to the procedure described in step 3 of Example 59.

EXAMPLE 73

25 3-(2-(5-benzyloxy-1-(2-naphthyl)methyl)indoliny)l)methylthioacetamidobenzoic acid

Step 1: Ethyl 3-(2-(5-benzyloxy-1-(2-naphthyl)methyl)indoliny)l)methylthioacetamidobenzoate

30 A mixture of 3-(2-(5-benzyloxy)indoliny)l)methylthioacetamidobenzoate (0.2g, 0.42 mmol), prepared in step 6 of Example 17, 2-(bromomethyl)naphthalene (0.1 g, 0.42 mmol) and potassium carbonate (0.17 g, 1.26 mmol) in N,N-dimethylformamide (2 mL) was stirred at room temperature overnight. Next the reaction was diluted with ethyl acetate and water,

extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using 2:1 hexane:ethyl acetate to yield 0.22 g of product (85 %, TLC = 0.5 Rf in 2:1 hexane:ethyl acetate).

5     Step 2:

The titled compound was prepared according to the procedure described in step 3 of Example 59.

10

EXAMPLES 74 and 75 in Table 6 were prepared according to the procedures described in Example 73.

15     EXAMPLE 76

2-(2-(-5-Benzyloxy-1-(2-naphthyl)methyl)indoliny)methylthiobenzoic acid

20     Step 1: 2-(2-(-5-Benzyloxy-1-(1,1-dimethyl)ethoxycarbonyl)indoliny)methyl  
methylsulfonate

tert-Butyl 1-(5-benzyloxy-2-hydroxymethyl)indolinyloformate (6.72 g, 19 mmol), prepared in step 2 of Example 17, was dissolved in  $\text{CH}_2\text{Cl}_2$  (80 mL, dried over  $\text{MgSO}_4$  before use). The clear yellow solution was cooled in a dry-ice bath.  $\text{Et}_3\text{N}$  (4.0 mL) was then added followed by methanesulfonyl chloride (2.0 mL). The reaction mixture was stirred for 25 2 h at  $-40^\circ\text{C}$  then quenched with  $\text{H}_2\text{O}$ . It was washed with saturated  $\text{NaHCO}_3$  (300 mL) and the aqueous layer extracted twice with  $\text{CH}_2\text{Cl}_2$ . The combined  $\text{CH}_2\text{Cl}_2$  layers were dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness to give the product (7.30 g, 89.1 % yield), which was used for the next reaction directly.

30

Step 2: Methyl 2-(2-(5-Benzyloxy-1-(1,1-dimethyl)ethoxycarbonyl)indoliny)methylthio  
benzoate

Mesylate (7.2 g, 1.8 mmol), prepared in step 1, was dissolved in DMF (50 mL). The clear light brown solution was degassed by vigorously bubbling with Ar for 30 min. Cesium carbonate (13.8 g) was added followed by methyl thiosalicylate (2.4 mL). The solution changed to a bright yellow and the suspension was stirred overnight. Methyl thiosalicylate (0.15 mL) was added to complete the reaction and the mixture was stirred overnight. The reaction was then quenched by the addition of saturated NaHCO<sub>3</sub> (400 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x) and the combined CH<sub>2</sub>Cl<sub>2</sub> solution was back-washed with H<sub>2</sub>O (200 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness to give the product (9.71 g, 99%).

Step 3: Methyl 2-(2-(5-Benzyloxy)indoliny)methylthiobenzoate

Ethyl acetate (75 mL, dried over MgSO<sub>4</sub> before use) was charged in a 500 mL round bottom flask. HCl gas was bubbled through and the EtOAc/HCl solution was cooled in an ice bath. Methyl ester (8.4 g), prepared in step 2, was dissolved in EtOAc (25 mL, dried over MgSO<sub>4</sub> before use). This solution was transferred to the HCl/EtOAc solution by syringe. The solution turned to red and was stirred in an ice bath. A white precipitate appeared in 1 h and the solution was stirred overnight to complete the reaction. The solid was collected by filtration, washed with dry EtOAc, suspended in saturated NaHCO<sub>3</sub> (175 mL) and stirred with EtOAc (400 mL). The milky emulsion gradually dissolved and the mixture changed to a clear solution. The layers were separated and the aqueous layer was extracted (2 x) with EtOAc, while the combined EtOAc layers were dried over MgSO<sub>4</sub>, filtered and evaporated to dryness to give the product (6.06 g, 90 % yield).

Step 4: Methyl 2-(2-(5-Benzyloxy-1-(4-benzyl)benzyl)indoliny)methylthiobenzoate

In a 50 mL round bottom flask, ester (1 g), prepared in step 3, was dissolved in DMF (6 mL). p-Benzylbenzyl bromide was added (1 eq) followed by K<sub>2</sub>CO<sub>3</sub> (1 eq). The reaction mixture was stirred overnight at room temperature. To complete the reaction additional p-benzylbenzyl bromide (0.5 eq) was added and the reaction was stirred for another 2 hours. After its completion, the reaction was diluted with H<sub>2</sub>O and extracted with EtOAc (2 x). The organic layers were combined and dried over MgSO<sub>4</sub>. The MgSO<sub>4</sub> was

filtered and the solvent was evaporated to give an oily material which was dried overnight on high vacuum to give the product (1.59 g, 109 % yield).

Step 5:

The ester (1.52 g), prepared in step 4, was dissolved in THF (10 mL) in a 50 mL round bottom flask. To it was added NaOH (1 eq, 2N) followed by MeOH (3 mL) and the reaction mixture was stirred overnight. Additional NaOH (0.3 eq) was added to complete the reaction and the mixture was stirred throughout the weekend. Then it was acidified and diluted with H<sub>2</sub>O and extracted with EtOAc (2 x). The organic layers were combined and dried over MgSO<sub>4</sub>. The MgSO<sub>4</sub> was filtered and the solvent was evaporated and dried on high vacuum to give a crude reddish solid. This solid was dissolved in EtOAc and hexane was added to precipitated the product. The resulting solid was filtered and the impure filter cake was combined with the filtrate and evaporated to dryness. This material was treated with EtOAc and EtOH. The resulting solid was filtered then suspended in EtOH, with stirring and heating at a low temperature. Then it was allowed to cool to room temperature. The suspension was filtered and washed with EtOH to give the titled product (280 mg, 19 % yield).

EXAMPLES 77, 78 and 79 in Table 6 were prepared according to the procedures described in Example 76.

EXAMPLE 80

4-(1-(5-Benzoyloxy-2-(bis-2,4-trifluoromethyl)benzyloxymethyl)indoliny)methylbenzoic acid

Step 1: Methyl 1-(5-Benzoyloxy-2-(hydroxymethyl)indoliny)methylbenzoate

2-(5-Benzoyloxy)indolinylmethanol (3.21 g, 12.6 mmol), prepared in DMF (20 mL), methyl 4-(bromomethyl)benzoate (2.88 g, 14.5 mmol) and potassium carbonate (1.77 g, heated to 125 °C before use) were mixed and stirred at room temperature for 2 h. The reaction was diluted with 100 mL of H<sub>2</sub>O and extracted three times with EtOAc. The combined EtOAc layers were evaporated to dryness to give the crude product (5.66 g). The

crude material was purified on a silica gel column using hexane:ethyl acetate 3:1 to 2:1. The appropriate fractions were combined, evaporated to dryness and further dried on high vacuum to the product (3.00 g, 64%).

5     Step 2: Methyl 4-(1-(5-Benzyloxy-2-(bis-2,4-trifluoromethyl)benzyloxymethyl)indoliny)  
          methylbenzoate

          Ester (700 mg), prepared in step 1, and bis-(2,4-trifluoromethyl)benzyl bromide  
          (0.35 mL) were dissolved in DMF (5 mL). The resulting clear yellow solution was cooled in  
10     an ice bath and then NaH (85 mg) was added in small portions over a period of 5 minutes.  
          The suspension was stirred at 0°C for 4 h. To complete the reaction, another 0.35 mL of  
          2,4-bis(trifluoromethyl)-benzyl bromide was added and the stirring was continued for another  
          3 h 40 min. The reaction was then diluted with H<sub>2</sub>O and extracted three times with EtOAc.  
          The combined EtOAc layers were evaporated to give a crude product which was then purified  
15     on a silica gel column using hexane:ethyl acetate 8:1. The appropriate fractions were  
          combined and evaporated to dryness to give the product (0.417 g, 38.2 % yield).

Step 3:

20           The titled compound was prepared according to the procedure described in step 5 of  
          Example 76.

EXAMPLES 81 and 82 in Table 6 were prepared according to the procedures described in  
25     Example 80.

EXAMPLE 835-(2-(1-(2,4-Bis(trifluoromethyl)benzyl)indoliny)carboxamido-1,3-benzenedicarboxylic acid5     Step 1: 2-(1-(2,4-Bis(trifluoromethyl)benzyl)indoliny)carboxylic acid

2-Indoliny)carboxylic acid (0.43 g, 2.6 mmol) was dissolved in DMF (5 mL), placed under N<sub>2</sub>, and cooled to 0° C, the sodium hydride (0.26 g of a 60 % dispersion, 6.5 mmol) was added and stirring was continued for 1 hour at this temperature. 2,4-  
10     Bis(trifluoromethyl)benzyl bromide (1.22 mL, 6.5 mmol) was next added and the reaction was warmed to room temperature overnight. The reaction was then diluted with 1/2 saturated ammonium chloride/ethyl acetate, the aqueous layer was extracted with ethyl acetate (3X), the organic layers were dried over magnesium sulfate and concentrated. The crude  
15     product was purified via chromatography (hexane:ethyl acetate 9:1) to yield 0.96 g of the ester. The resulting ester (0.87 g, 0.141 mmol) was dissolved in THF/ methanol and then 1N sodium hydroxide (4.21 mL) was added and the resulting mixture was stirred 2 hours at RT, workup and purification via Chromatography (7:1 hexane:ethyl acetate with 1 % acetic acid) yielded 0.58 g of the product.

20     Step 2:

The acid (0.25 g, 0.64 mmol), prepared in step 1, EDCI (0.16 g, 0.83 mmol), DMAP (7 mg, 0.06 mmol) and dimethyl 5-aminoisophthalate (0.16 g, 0.77 mmol) were dissolved in THF (2 mL) and refluxed 16 hours which yielded after aqueous workup 0.33 g  
25     of a crude product. The ester (0.29 g, 0.50 mmol) was dissolved in THF/ methanol and then 1N sodium hydroxide (1.5 mL) was added and the resulting mixture was stirred 16 hours at RT, workup and purification via Chromatography (1:1 hexane:ethyl acetate with 1 % acetic acid) yielded 0.22 g of the titled compound.

30

EXAMPLE 84



N-Methylsulfonyl-2-(1-(2,4-bis(trifluoromethyl)benzyl)indoliny)l)carboxamide

The acid (0.13g, 0.32 mmol), prepared in step 1 of Example 83, EDCI (0.07 g, 0.39 mmol), DMAP (4 mg, 0.03 mmol) and methylsulfonamide (0.04 g, 0.39 mmol) were dissolved in THF (5 mL) and refluxed 16 hours which yielded after workup (0.16 g), purification via Chromatography (98:2 dichloromethane:methanol) yielded 0.04 g of the titled compound (29%).

10 EXAMPLE 85N-Phenylsulfonyl-2-(1-(bis-2,4-trifluoromethyl)benzyl)indoliny)l)carboxamide

The titled compound was prepared according to the prodedure described in Example 84, but using phenylsulfonylamide.

EXAMPLE 86

20 5-(2-(5-Methoxybenzyloxy-1-(2,4-bis(trifluoromethyl)benzyl)indoliny)l)methylaminocarboxamido-1,3-benzenedicarboxylic acid

Step 1: 2-Trimethylsilylethyl 1-(5-benzyloxy-2-hydroxymethyl)indoliny)lformate

25 An oven-dried 1 L round bottom flask, equipped with a stir bar was charged with 2-(5-benzyloxy)indoliny)l)l)l)methanol (33.2 g, 130 mmol), prepared in step1 of Example 17, 2-(trimethylsilyl)ethyl p-nitrophenyl carbonate 36.8 g, 130 mmol), NEt<sub>3</sub> (38 ml, 273 mmol), and 300 mL of anhydrous DMF. The reaction mixture was stirred at 60°C for 28 hours and at room temperature overnight. The resulting solution was concentrated to dryness in vacuo, and 1 L of CHCl<sub>3</sub> and 200 mL of saturated NaHCO<sub>3</sub> solution were added. The layers were separated, and the organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude

material obtained (55.7 g) was purified by column chromatography on silica gel (eluant: 0-5 % MeOH in dichloromethane) to afford product (33.5 g, 60% yield).

Step 2: 2-Trimethylsilylethyl 1-(5-hydroxy-2-hydroxymethyl)indolinyformate

5

An oven-dried 500 mL Parr pressure flask was charged with the alcohol (30 g, 75 mmol), prepared in step 1, Pd/C (10 %, 2.2 g), 100 mL of MeOH, and 300 mL of EtOAc. After being shaken overnight in a Parr apparatus under H<sub>2</sub> atmosphere (50 psi), the reaction mixture was filtered through Florisil. The filtrate was concentrated to dryness on the rotary.

10 The crude material obtained (24 g) was purified by column chromatography on silica gel (eluant: 0-3 % MeOH in dichloromethane) to afford product (20.9 g, 90% yield).

Step 3: 2-Trimethylsilylethyl 1-(5-(4-methoxy)benzyloxy-2-hydroxymethyl)indolinyformate

15

An oven-dried 1 L round bottom flask, equipped with a stir bar was charged with the diol (27.1 g, 87.7 mmol), prepared in step 2, 4-methoxybenzyl chloride (Aldrich, 15 mL, 110 mmol), K<sub>2</sub>CO<sub>3</sub> (200 mesh, 30.4 g, 220 mmol), KI (Aldrich, 18.3 g, 110 mmol), and 800 mL of anhydrous acetonitrile. The reaction mixture was heated at reflux for 4 h. The solution was allowed to cool to room temperature and water (800 mL) and CHCl<sub>3</sub> (1.5 L) were added. The layers were separated, and the aqueous phase was extracted with CHCl<sub>3</sub> (800 mL). The combined extracts were washed with water (200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude material obtained (45 g) was purified by column chromatography on silica gel (eluant: 20-25 % EtOAc in hexane), and recrystallization from EtOAc/Hexane to afford product (22.2 g, 59% yield).

25

Step 4: 2-Trimethylsilylethyl 1-(5-(4-methoxy)benzyloxy-2-bromomethyl)indolinyformate

To a solution of 3.0 g (6.4 mmol) of the alcohol, prepared in step 3, in 30 mL of dichloromethane was added 2.53 g (7.6 mmol) of carbon tetrabromide and 3.15 g (7.6 mmol) of 1,3-bis(diphenylphosphino)propane. The reaction was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl, and the product was extracted with dichloromethane. The combined organic extracts were washed with brine and dried

30

over  $\text{MgSO}_4$ . The crude product was purified by flash chromatography using hexane:ethyl acetate 3:2 to afford 1.51 g of the product.

Step 5: 2-Trimethylsilylethyl 1-(5-(4-methoxy)benzyloxy-2-azidomethyl)indolinyloformate

5

To a solution of 1.4 g (2.6 mmol) of the bromide, prepared in step 4, in 15 mL of dimethylformamide was added 0.51 g (7.9 mmol) of sodium azide. The reaction was heated to 75 °C, and was stirred for 18 h. The reaction was quenched with water, and the product was extracted with ethyl acetate. The combined organic layers were washed with water,  
10 brine and dried over  $\text{MgSO}_4$ . The crude product was purified by flash chromatography using hexane:ethyl acetate 4:1 to afford 1.08 g of the product.

Step 6: 2-Trimethylsilylethyl 1-(5-(4-methoxy)benzyloxy-2-aminomethyl)indolinyloformate

15

To a solution of 0.88 g (1.9 mmol) of the azide, prepared in step 5, in 20 mL of ethanol was added 90 mg (10%/wt) of Pd/CaCQ. The mixture was placed under atmospheric hydrogen, and was stirred for 18 h. The reaction was then filtered through a pad of celite and the organic phase was concentrated. The crude product was purified by flash chromatography using 10% MeOH/ $\text{CH}_2\text{Cl}_2$  to afford 0.717 g of the product.

20

Step 7: Methyl 5-(2-(5-Methoxybenzyloxy-1-(2-trimethylsilyloxy)ethoxycarbonyl)indolinylo)methylaminocarboxamido-1,3-benzenedicarboxylate

To a solution of 0.164 g (0.6 mmol) of triphosgene in 5 mL of dichloromethane was  
25 added a solution of 0.31 g (1.5 mmol) of dimethyl-5-aminoisophthalate and 0.39 g (3.0 mmol) of diisopropylethylamine in 20 mL of dichloromethane over a 30 minute period via a syringe pump. The reaction was stirred for 1 h at room temperature following the addition, and then a solution of 0.64 g (1.5 mmol) of the amino, prepared in step 6, in 5 mL of dichloromethane was added in one portion. The reaction was stirred for 2 h, and then  
30 quenched with water. The product was extracted with ethyl acetate, and the combined organic layers were washed with water, saturated aqueous  $\text{NaHCO}_3$ , brine and dried over

MgSO<sub>4</sub>. The crude product was purified by flash chromatography using 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford 0.78 g of the product.

Step 8: Methyl 5-(2-(5-Methoxybenzyloxy)indolinyl)methylaminocarboxamido-1,3-

5 benzenedicarboxylate

To a solution of 0.485 g (0.7 mmol) of the ester, prepared in step 7, in 20 mL of acetonitrile was added 2.2 mL (2.2 mmol) of a 1.0 M tetrabutylammonium fluoride solution in THF. The reaction was stirred at room temperature for 18 h. The reaction was quenched  
10 with brine, and the product was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous NH<sub>4</sub>Cl, brine and dried over MgSO<sub>4</sub>. The crude product was purified by flash chromatography using 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford 0.342 g of the product.

15 Step 9: Methyl 5-(2-(5-Methoxybenzyloxy-1-(bis-2,4-trifluoromethyl)benzyl)indolinyl)  
methylaminocarboxamido-1,3-benzenedicarboxylate

To a solution of 0.15 g (0.3 mmol) of the indoline diester, prepared in step 8, in 5 mL of dimethylformamide was added 0.097 g (0.3 mmol) of 2,4-bis(trifluoromethyl)benzyl  
20 bromide and 0.12 g (0.9 mmol) of potassium carbonate. The reaction was stirred at room temperature for 18 h. The reaction was quenched with water, and the product was extracted with ethyl acetate. The combined organic extracts were washed with water, brine and dried over MgSO<sub>4</sub>. The crude product was purified by flash chromatography using hexane:ethyl acetate 1:1 to afford 0.066 g of the product.

25

Step 10:

To a solution of 0.063 g (0.1 mmol) of the diester, prepared in step 9, in 5 mL of tetrahydrofuran was added 0.8 mL (0.8 mmol) of a 1.0 N NaOH solution and 0.5 mL of  
30 methanol. The reaction was stirred at room temperature for 18 h. The organic solvents were evaporated, and the resulting solid was suspended in water and acidified to pH 3 with 10% HCl. The product was extracted with ethyl acetate, and the combined organic extracts were

washed with water, brine and dried over  $\text{MgSO}_4$ . The crude product was purified by flash chromatography using 5%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  to afford 0.049 g of the titled compound.

- 5     EXAMPLE 87 was prepared according to the procedure described in Example 86, but using 4-(3,5-bis(trifluoromethyl)phenoxy)methyl)benzyl bromide.

10

#### INTERMEDIATE 1

##### Methyl 4-methoxy-3-thioacetamidobenzoate

15

##### Step 1: Bis(methyl 4-methoxy-3-dithioacetamidobenzoate)

- 20     A 2-L oven-dried round bottom flask fitted with a magnetic stirring bar was charged with Dithioacetic acid (10.2-15.5 g, 56-85 mmol) and anhydrous  $\text{CH}_2\text{Cl}_2$  (50 mL). Oxalyl chloride (2.1 mol equiv.) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 4-5 h. Methyl 4-methoxy-3-amidobenzoate (2.1 mol equiv.) in anhydrous  $\text{CH}_2\text{Cl}_2$  (300-500 mL) and DMAP (0.1 mol equiv.) were added at room temperature.  $\text{NEt}_3$  (4.2 mol equiv.) was added dropwise over 30 min. After stirring overnight at room temperature the reaction mixture was washed with 1 N HCl solution (2 x 25     300 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel using hexane:ethyl acetate = 5:1 afford desired product in 56% yield.

##### Step 2:

30

A 1-L round bottom flask fitted with a magnetic stirring bar was charged with disulfide, prepared in step 1, (15.7-26.3 g, 36.6-57.5 mmol) and  $\text{PPH}_3$  (1.1 mol equiv.). The

reactants were suspended in dioxane/H<sub>2</sub>O (4/1, 375-500 mL) and concentrated HCl solution (5 drops) was added. The reaction mixture was heated at 40°C until all disulfide was consumed. Solvents were removed in vacuo. The residue was purified immediately by column chromatography on silica gel using hexane : ethyl acetate 2:1 to afford the titled product in 89% yield.

## INTERMEDIATE 2

### 10 Methyl 5-thioacetamido-1,3-benzenedicarboxylate

The titled compound was synthesized according to the procedures described in Intermediate 1 using 5-amino-1,3-benzenedicarboxylate.

15

## UINTERMEDIATE 3

### Methyl 2-(3-amino-4-methoxyphenyl)-2-methoxyacetate

### 20 Step 1: Methyl 2-(3-nitro-4-methoxyphenyl)acetate

An oven-dried 2-L, 3-neck round bottom flask, equipped with a mechanical stir motor, a low-temperature thermometer and an equalizing dropping funnel, was charged with acetic anhydride (631 mL) and subsequently cooled to -78°C. Fuming nitric acid (Baker, 25 90%, 27 mL) was added dropwise via the dropping funnel protected with a drying tube filled with CaCl<sub>2</sub>. After addition was completed, the reaction temperature was allowed to warm to 20 °C over 1 h. The reaction mixture was cooled to -78°C again and added 4-methoxyphenylacetic acid (50 g, 0.28 mol) dropwise via the dropping funnel. After stirring at -50 °C for 1 h., the reaction mixture was allowed to warm to -30°C over 20 min. and then 30 cooled to -50 °C again. The reaction mixture was quenched with H<sub>2</sub>O (500 mL) at -50 °C and warmed up to room temperature and stirred for 0.5 h. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (500 mL) and H<sub>2</sub>O. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 500

mL). The combined  $\text{CH}_2\text{Cl}_2$  extracts were concentrated in vacuo to give a yellow oil. This was added slowly to a 2 M solution of NaOH (2 L) cooled at  $0^\circ\text{C}$  and stirred at room temperature overnight. The reaction mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  (500 mL) and  $\text{H}_2\text{O}$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 500 mL). The combined  $\text{CH}_2\text{Cl}_2$  extracts were stirred with 2 M NaOH solution (1 L) for 1 h. The layers were separated and the organic layer was washed with  $\text{H}_2\text{O}$  (500 mL), brine (500 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvents were removed in vacuo to afford crude product as a light yellow solid (56 g). Purification by recrystallization from MeOH (600 mL) gave product. Yield 48 g (77%).

10

Step 2: Methyl 2-(3-nitro-4-methoxyphenyl)-2-hydroxyacetate

A 25-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with ester (2.3 g, 10 mmol), prepared in step 1, and anhydrous THF (100 mL). The reaction mixture was cooled to  $-78^\circ\text{C}$  and a solution of  $\text{NaN}(\text{SiMe}_3)_2$  (1.0 M in THF, 12 mL, 12 mmol) was added dropwise over 10 min. After stirring at  $-78^\circ\text{C}$  for 30 min., the deep purple solution was added dropwise a solution of racemic camphor sulfonyloxaziridine (3.4 g, 15 mmol), prepared by mixing the commercially available (1S)-(+)-(10-camphorsulfonyl)oxaziridine (1.7 g) and (1R)-(-)-(10-camphorsulfonyl)oxaziridine (1.7 g) in 50 mL THF. After stirring at  $-78^\circ\text{C}$  for 30 min., the reaction mixture was quenched with sat.  $\text{NH}_4\text{Cl}$  solution (45 mL) at  $-78^\circ\text{C}$  and then allowed to warm to room temperature. The reaction mixture was partitioned between ether (250 mL) and  $\text{H}_2\text{O}$  (50 mL). The aqueous layer was extracted with ether (3 x 250 mL). The combined ether extracts were washed with brine (250 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvents were removed in vacuo. Purification by column chromatography on silica gel (eluant: 50% AcOEt in hexane) afforded desired product. Yield 2.2 g (88%).

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Step 3: Methyl 2-(3-nitro-4-methoxyphenyl)-2-methoxyacetate

A 10-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with alcohol (0.30 g, 1.24 mmol), prepared in step 2, AgO (0.68 g, 3.0 mmol) and toluene (3 mL). To this was added  $\text{CHI}_3$  (0.36 g, 5.75 mmol) dropwise. The reaction flask

30

was capped tightly and placed into a sonication chamber. The reaction mixture was sonicated for 18 h while stirring at room temperature. The reaction mixture was filtered through Celite and concentrated in vacuo to dryness. The residue was purified by column chromatography on silica gel (eluant: 30% AcOEt in hexane) to afford desired product. Yield 0.26 g (82%).

5

Step 4:

A 100-mL oven-dried round bottom flask fitted with a magnetic stirring bar and a three way adapter, connecting to a hydrogen balloon and a water aspirator was charged with nitro compound (0.7 g, 2.6 mmol), 5% Pd on Carbon (10% by weight) and MeOH (20 mL). The reaction flask was placed under vacuum via the water aspirator and subsequently filled with H<sub>2</sub>. This was repeated three times. The reaction mixture was stirred for 18 hours under positive H<sub>2</sub> pressure until all starting material was reacted. The reaction mixture was filtered through Celite and concentrated in vacuo to dryness. The residue was purified by column chromatography on silica gel using 10% ethyl acetate in dichloromethane to afford the titled compound (0.57 g, 97%)

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INTERMEDIATE 4

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Methyl 2-(3-amino-4-methoxyphenyl)-2-tert-butyl dimethylsilyloxyacetate

A 25-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with alcohol (0.30 g, 1.24 mmol), prepared in step 2 of Intermediate 3 and anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The reaction mixture was cooled to 0°C and added 2,6-lutidine (dried over NaOH pellet, 0.36 mL, 3.11 mmol) followed by addition of BuMe<sub>2</sub>SiOTf (0.43 mL, 1.87 mmol) dropwise. After stirring at 0°C for 30 min., the reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and H<sub>2</sub>O (15 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were removed in vacuo. Purification by column chromatography on silica gel (eluant: 30% AcOEt in hexane) afforded desired product. Yield 0.42 g (95%).

25

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Step 2:

The titled compound was prepared from nitro compound of step 1 according to the procedure described in step 4 of Intermediate 3.

5

INTERMEDIATE 5Methyl 2-(3-amino-4-methoxyphenyl)acetate

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The titled compound was prepared from nitro compound, prepared in step 1 of Intermediate 3, according to the procedure described in step 4 of Intermediate 3.

15 INTERMEDIATE 6Methyl 2-(3-amino-4-methoxyphenyl)-2-methylacetateStep 1: Methyl 2-(3-nitro-4-methoxyphenyl)-2-methylacetate

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A 25-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with redistilled diisopropylamine (0.84 mL, 6.0 mmol) and anhydrous THF (10 mL) and cooled to 0°C. A solution of n-BuLi (2.5 M in hexane, 2.4 mL, 6.0 mmol) was added dropwise over 5 min. After stirring at 0°C for 15 min., the reaction temperature was allowed to cool to -78°C and added a solution of ester (1.13 g, 5.0 mmol), prepared in step 1 of Intermediate 3, in 10 mL THF dropwise. After stirring at -78°C for 45 min., dimethylsulfate (1.60 g, 12.5 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and H<sub>2</sub>O (50 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were removed in vacuo. Purification by column

chromatography on silica gel (eluant: 30% AcOEt in hexane) afforded 0.7 g of product (58%).

Step 2:

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The titled compound was prepared from nitro compound, prepared in step 1, according to the procedure described in step 4 of Intermediate 3.

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INTERMEDIATE 7Methyl 2-(3-amino-4-methoxyphenyl)-2-allylacetate5     Step 1: Methyl 2-(3-nitro-4-methoxyphenyl)-2-allylacetate

This compound was synthesized from ester, prepared in step 1 of Intermediate 3, according to the procedure described in step 1 of Intermediate 6, but using allyl bromide.

10     Step 2:

A 25-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with ester (0.30 g, 1.13 mmol), prepared in step 1,  $\text{SnCl}_4 \cdot 2\text{H}_2\text{O}$  (1.28 g, 5.66 mmol) and EtOH (5 mL). The reaction mixture was heated at 70°C for 30 min. The reaction  
15     mixture was cooled to room temperature and poured onto ice/water (20 mL) and basified with saturated  $\text{Na}_2\text{CO}_3$  solution to pH = 8. AcOEt (50 mL) was added. The resulting emulsion was filtered through Celite. The filtrate was partitioned between AcOEt (20 mL) and  $\text{H}_2\text{O}$  (15 mL). The aqueous layer was extracted with AcOEt (3 x 50 mL). The combined AcOEt  
20     extracts were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvents were removed in vacuo. Purification of the residue by column chromatography on silica gel (eluant: 10% AcOEt in  $\text{CH}_2\text{Cl}_2$ ) afforded the titled compound. Yield 0.16 g (60%).

INTERMEDIATE 8

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2,4-Bis(1,1-dimethylpropyl)phenoxyacetic acid

The 2,4-bis(1,1-dimethyl)propylphenol (12 g, 51.2 mmol) in dimethylformamide (100 mL) was cooled to -30° C, treated with solid potassium bis(trimethylsilyl)amide (12.3g, 61.5  
30     mmol), stirred for 30 minutes and then methyl bromoacetate (5.7 mL, 61.5 mmol) was added, the reaction was stirred 1 hour at this temperature and five hours after removal of the cooling bath, workup yielded (16.6g, ≈100%) a yellow oil. The oil was dissolved in

THF/methanol and treated with 1N sodium hydroxide (155 mL) and stirred for 48 hours. The reaction was concentrated, diluted with water, acidified to pH 4 with concentrated HCl, extracted with ethyl acetate (4X), dried over magnesium sulfate and concentrated. Crystalization from ethyl acetate and hexane yielded 12.85 g of the titled compound. (86%).

5

#### INTERMEDIATE 9

##### 4-Benzylphenoxyacetic acid

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The titled compound was prepared from 4-benzylphenol according to the procedure described in of Intermediate 8.

#### INTERMEDIATE 10

##### 2-Naphthoxyacetic acid

The titled compound was prepared from 2-naphthol according to the procedure described in of Intermediate 8.

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#### INTERMEDIATE 11

##### 3,5-Bis(trifluoromethyl)phenoxyacetic acid

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The titled compound was prepared from 3,5-bis(trifluoromethyl)phenol according to the procedure described in of Intermediate 8.

#### INTERMEDIATE 12

##### Methyl 5-amino-3-(N,N-dimethyl)carbamoylbenzoate

Step 1: Methyl 5-nitro-3-(N,N-dimethyl)carbamoylbenzoate

A 100-mL oven-dried round bottom flask fitted with a magnetic stirring bar was charged with 5-nitro-3-methoxycarbonylbenzoic acid (3.15 g, 10 mmol), DMF (1 drop),  
5 anhydrous  $\text{CH}_2\text{Cl}_2$  (70 mL), and oxalyl chloride (3.7 mL, 42.3 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo to afford acid chloride as a white solid. This was used immediately in the next step without further purification.

An oven-dried round bottom flask fitted with a magnetic stirring bar was charged  
10 with above prepared acid chloride (14 mmol), anhydrous  $\text{CH}_2\text{Cl}_2$  (50 mL), and dimethylamine hydrochloride (70 mmol).  $\text{NEt}_3$  (2 mL, 144 mmol) was added dropwise. After stirring at room temperature for 30-60 min excess  $\text{NEt}_3$  (1 mL, 72 mmol) was added and stirring was continued. After 30-60 min the solution was washed with saturated  $\text{Na}_2\text{CO}_3$  solution (2 x 20 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuo to afford 3.3 g of  
15 product. This was used in the next step without further purification.

Step 2:

The titled compound was prepared from nitro compound, prepared in step 1,  
20 according to the procedure described in step 4 of Intermediate 3.

INTERMEDIATE 13

25 Methyl 5-amino-3-acetylbenzoate

Step 1: Methyl 5-nitro-3-acetylbenzoate

A 250-mL oven-dried round bottom flask fitted with a magnetic stirring bar was  
30 charged with di-tert-butyl malonate (2.16 g, 10 mmol), anhydrous toluene (50 mL), and NaH (60% suspension in mineral oil, 0.88 g, 22 mmol). The reaction mixture was heated at  $80^\circ\text{C}$  for 1 h. A solution of methyl 5-nitro-3-chloroformylbenzoate (10 mmol), prepared in step 1

of Intermediate 12, in anhydrous toluene (20 mL) was added and heating was continued for 2 h. The reaction mixture was cooled to room temperature and p-toluenesulfonic acid (0.21 g, 1.2 mmol) was added. The resulting mixture was filtered and the oily residue was washed with toluene until a white solid was left. The filtrates were combined and the solvent was removed in vacuo. The resulting oil was dissolved in anhydrous toluene (50 mL) and p-toluenesulfonic acid (0.3 g, 1.74 mmol) was added. After heating to reflux for 18 h the reaction mixture was allowed to cool to room temperature, washed with saturated  $\text{Na}_2\text{CO}_3$  solution (2 x 25 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuo. The crude material was purified by column chromatography on silica gel (eluant:  $\text{CH}_2\text{Cl}_2$ ) to afford product. Yield 1.06 g (50%).

#### Step 2:

The titled compound was prepared from nitro compound, prepared in step 1, according to the procedure described in step 4 of Intermediate 3.

#### INTERMEDIATE 14

Methyl 5-amino-3-(1-tert-butyl(dimethylsilyloxy)ethyl)benzoate

#### Step 1: Methyl 5-nitro-3-(1-hydroxy)ethylbenzoate

An oven-dried round bottom flask fitted with a magnetic stirring bar was charged with compound methyl 5-nitro-3-acetylbenzoate (0.5 g), prepared in step 1 of Intermediate 13,  $\text{BH}_3$ , THF (1 M solution in THF, 5 mol equiv.), and anhydrous THF. After stirring at room temperature for 24 h,  $\text{H}_2\text{O}$  (20 mL) was added and the solution was concentrated in vacuo. The residue was taken in  $\text{H}_2\text{O}$  (20 mL) and extracted with  $\text{CHCl}_3$  (3 x 100 mL). The combined  $\text{CHCl}_3$  extracts were washed with saturated  $\text{Na}_2\text{CO}_3$  solution (20 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuo to afford product. This was used in the next step without further purification.

Step 2: Methyl 5nitro-3-(1-tert-butyldimethylsilyloxy)ethylbenzoate

An oven-dried round bottom flask fitted with a magnetic stirring bar was charged with alcohol (0.5g, 5 mmol), prepared in step 1, tert-BuMe<sub>2</sub>SiCl (1.3 mol equiv.), imidazole (2.15 mol equiv.), and anhydrous THF. After stirring at room temperature for 28 hours the solvent was removed in vacuo. The residue was taken in H<sub>2</sub>O (50 mL) and extracted with CHCl<sub>3</sub> (2 x 100 mL). The combined CHCl<sub>3</sub> extracts were washed with H<sub>2</sub>O (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was removed in vacuo. The crude material was purified on silica gel using 25%-50% dichloromethane in hexane to afford the product (0.69 g, 91%).

Step 3:

The titled compound was prepared from nitro compound, prepared in step 2, according to the procedure described in step 4 of Intermediate 3.

INTERMEDIATE 15Methyl 4-methoxy-3-(2-thioethyl)aminobenzoateStep 1: Bis(2-bromoethyl)disulfide

The dithioethanol (0.79 mL, 6.48 mmol), carbon tetrabromide (4.3 g, 13.0 mmol) and 1,3 bis(diphenylphosphino)propane (5.34 g, 13.0 mmol) were weighed into a flask and flushed with nitrogen and then taken up in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and stirred for 16 hours, workup consisted of pouring into 1/2 saturated ammonium chloride and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X) dry magnesium sulfate and concentrated to yield (9.0 g) of a crude product that was chromatographed (Hexane:Ethyl acetate 9:1) to yield 1.49 g of product.

Step 2: Bis-(methyl 4-methoxy-3-(2-dithioethyl)aminobenzoate

Bromide (0.39 mg, 1.387 mmol), prepared in step 1, and methyl 3-amino-4-methoxy benzoate (1.00 g, 5.51 mmol) were added into a flask, flush with nitrogen and take up in DMF (5 mL) and then heat to 60° C for 24 hours at which time the reaction was diluted with ethyl acetate and quenched into water, extracted with ethyl acetate (3X), the combined  
5 organic layers were washed with water (3X), dried and concentrated to yield 1.27 g of a product that was purified by chromatography (hexane:ethyl acetate 5:1 to 3:1) to yield 0.15 g of the desired product.

Step 3:

10

The disulfide (0.15 g, 0.24 mmol), prepared in step 2, and the triphenylphosphine (0.14 g, 0.53 mmol) were taken up in THF (3 mL). H<sub>2</sub>O (0.3 mL) and two drops of conc. HCl were added and the resulting mixture was stirred at 40° C for 2 hours, the reaction was diluted with water and ethyl acetate, extracted with ethyl acetate (3 X) and dried over  
15 magnesium sulfate to yield 0.27 g of a crude product that was purified by chromatography (hexane:ethyl acetate 9:1 to 6:1) to yield 0.11 g of the titled compound.



Methods of Synthesis for Examples 88-135

Additional compounds of the invention can be made according to the following methods. Specific examples of synthesis of compounds pursuant to these methods are also disclosed below.

**Method A**

The aldehyde is reacted with the alpha-carbon of a heterocycle such as 2,4-thiazolidinedione or rhodanine or 2-thiohydantoin in the presence of a base such as potassium carbonate or potassium hydroxide in a solvent system such as water:ethanol or ethanol. The resulting product may then be N-alkylated with a base such as sodium hydride in a solvent such as DMF or DMSO. The final acid may then be realized by cleavage of the ester with hydrogen fluoride in a solvent such as acetonitrile.

**Method B**

Indole-2-carboxylic acid was alkylated with an appropriate alkyl bromide which was then subjected to Suzuki coupling conditions using  $\text{Pd}(\text{PPh}_3)_4$  as a catalyst in a mixed solvent (ethanol-benzene-water) at elevated temperature to give the 1-alkyl-5-substituted indole.

**Method C**

The starting material for the inhibitors in this class, 2-Ethoxycarbonyl-5-benzyloxyindole **I**, was deprotonated with a suitable base such as sodium hydride and alkylated on the nitrogen atom with selected electrophiles such as alkyl or benzyl halides to provide compounds **II**. Saponification of the ester functionality with a base such as aqueous sodium hydroxide in miscible solvents such as tetrahydrofuran and methanol gave inhibitors **III**. Further extensions at the 2-position were carried out through amide formation of the acid functionality via acid chloride formation with a suitable reagent such as oxalyl chloride and reaction with an amino-ester in the presence of a base such as pyridine in a suitable solvent such as methylene chloride. Saponification provided the chain extended acid moiety **V**.

**Method D**

Acid isosteres such as tetrazole were prepared from the carboxylic acids **I** via the nitriles **III**. Conversion to the nitriles was accomplished through primary amide formation of the acid functionality via the acid chloride with a suitable reagent such as oxalyl chloride and reaction with ammonia followed by a dehydration sequence using a suitable reagent such as oxalyl chloride and a base such as pyridine. The nitriles such as **III** could be converted to the tetrazoles by reaction with an azide source such as sodium azide in an appropriate high boiling point solvent such as N-methyl pyrrolidinone to give compounds such as **IV**.

**Method E**

Other acid isosteres such as the thiazolidinedione group with longer carbon atom bridges were prepared through a sequence involving the unsaturated aldehyde moiety at the 2-position such as compound **IV**. Partial reduction of the ester group in **I** with a suitable reagent such as diisobutyl aluminum hydride or reduction to a hydroxy group with a suitable reagent such as lithium aluminum hydride followed by oxidation to the aldehyde with a suitable oxidizing agent gave the aldehyde **II**. A Horner-Wittig reaction with trimethoxyphosphonoacetate in a suitable solvent such as tetrahydrofuran gave the unsaturated ester **III**, which was converted to the aldehyde **IV** under the conditions described for **II**. The aldehyde could then be transformed to the thiazolidinedione **V** using a base such as piperidine and isolated with an acid such as acetic acid.

**Method F**

2-Indolyl carboxylic acid ethyl ester **I** is deprotonated with a strong base such as sodium hydride (NaH) in THF, and then reacted with a suitable alkyl bromide to give **VI**. Hydrolysis of **VI** with aqueous base such as sodium hydroxide and reaction with aniline or a substituted aniline in the presence of a carbodiimide such as dimethylaminopropylethyl carbodiimide hydrochloride (EDCI) in a suitable solvent such as dichloromethane affords amide **VII**. Amide **VII** is hydrolyzed to corresponding acid **VIII** in a aqueous base such as sodium hydroxide.

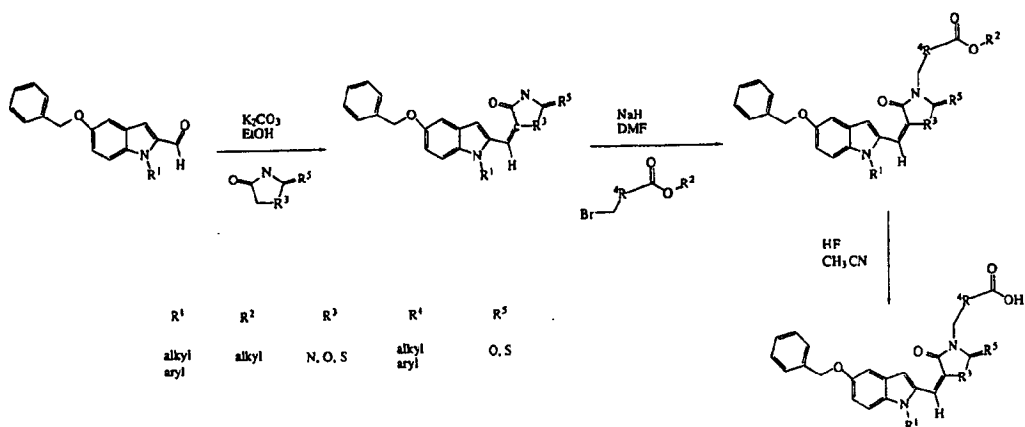
**Method G**

Aldehyde IX is prepared from Indol-2-carboxylic acid ethyl ester I in two steps: (1) Reduction with lithium aluminium hydride or other hydride in a suitable solvent such as THF at 0°C and (2) oxidation with an oxidizing reagent such as manganese dioxide in a solvent such as THF. Aldehyde IX can be alkylated by a suitable alkyl bromide (or iodide), such as benzyl bromide or ethyl iodide in the presence of a strong base such as sodium hydride or KHMDS in a solvent such as DMF to yield indole X. Indole X can be converted to an unsaturated acid XI in two steps: (1) Wittig reaction with a suitable reagent such as trimethyl phosphonoacetate in the presence of a base such as sodium hydride in a solvent such as THF and (2) Hydrolysis by aqueous sodium hydroxide.

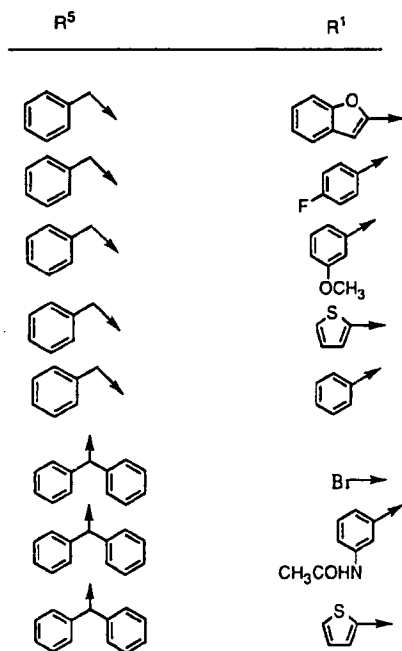
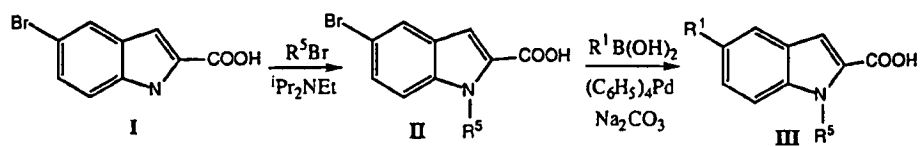
#### Method H

Indole I can be converted to II in two steps: (1) reduction with LAH in a solvent such as THF and (2) silylation with t-butyldimethylsilyl chloride (TBDMSCl) in a solvent such as dichloromethane or DMF in the presence of a base such as imidazole. Treatment of II with Grignard reagent such as ethyl magnesium bromide in a solvent such as THF at -60°C, acylation of the resulting magnesium salt with a suitable acyl chloride such as acetyl chloride in ether and finally, alkylation on the nitrogen with an alkyl halide such as ethyl bromide in the presence of a strong base such as NaH in DMF affords ketone III. The silyl group on III is removed using tetrabutylammonium fluoride in a solvent such as THF, the resulting alcohol is then converted to bromide using carbon tetrabromide and bis(diphenylphosphino)ethane in a solvent such as dichloromethane to yield bromide IV. Displacement of the bromine of IV with a thiol compound in the presence of a base such as cesium carbonate, or with an alcohol in the presence of a strong base such as NaH in DMF affords V (sulfide or ether respectively).

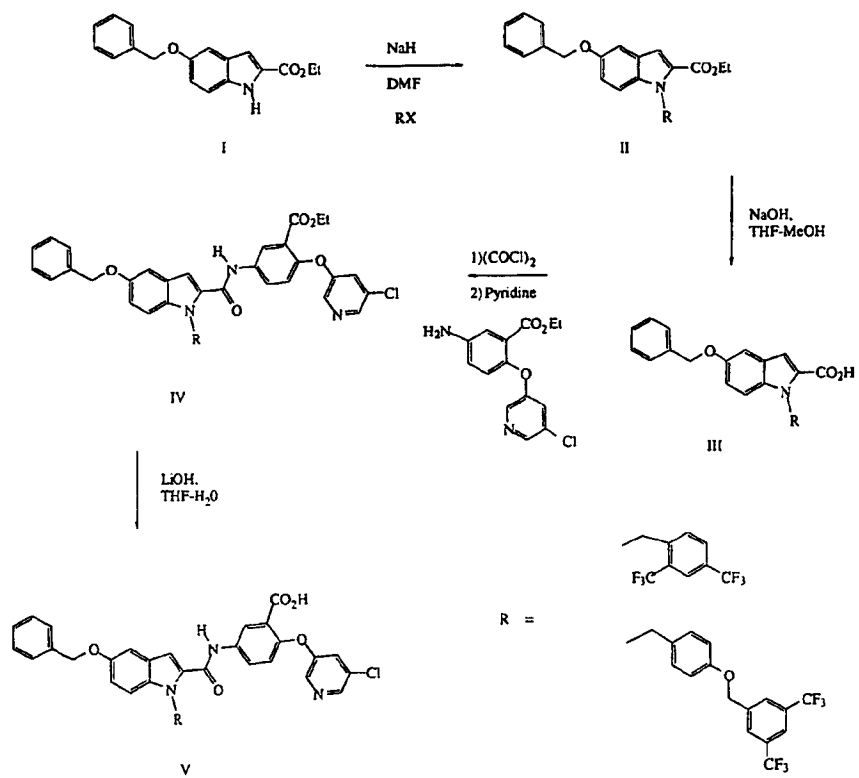
## Method A



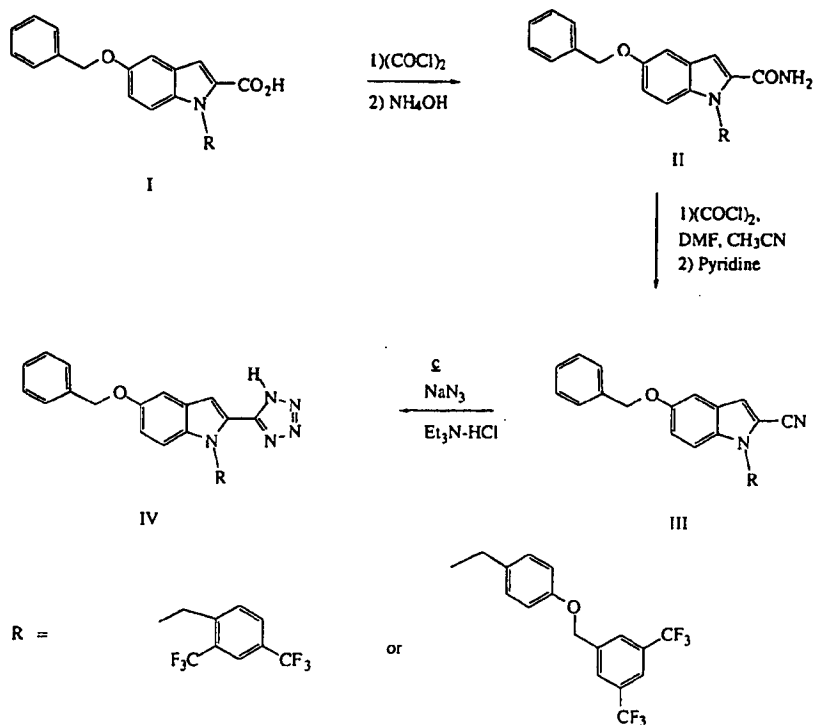
## Method B



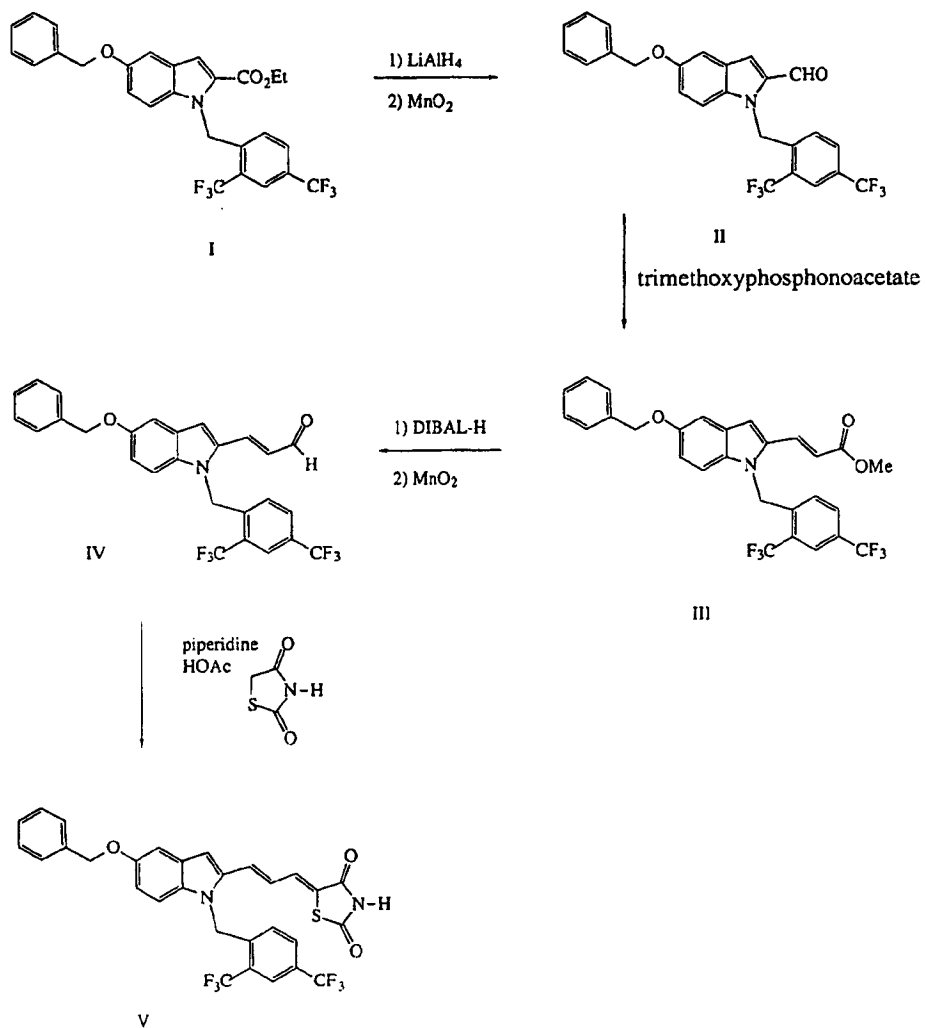
## Method C



## Method D

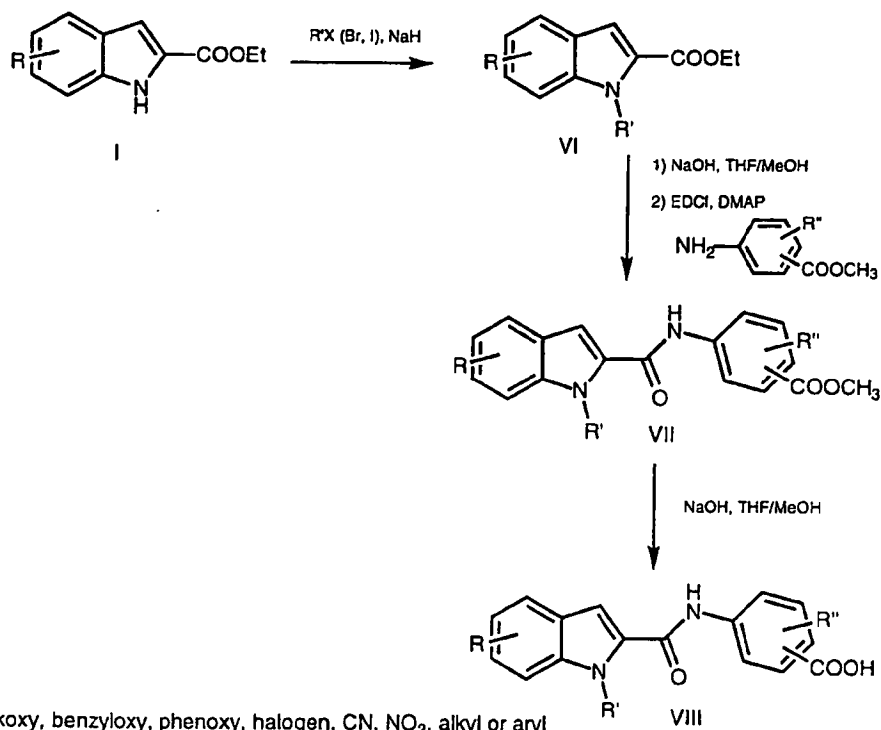


## Method E





## METHOD F

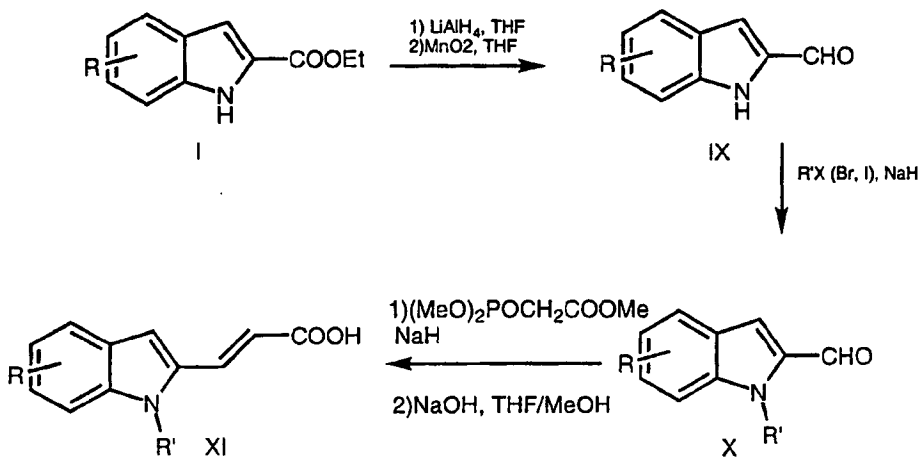


R = alkoxy, benzyloxy, phenoxy, halogen, CN, NO<sub>2</sub>, alkyl or aryl

R' = alkyl, benzyl, alkenyl, alkynyl

R'' = halogen, CN, alkyl, alkoxy, alkoxycarbonyl, amido, acyl, H, OH

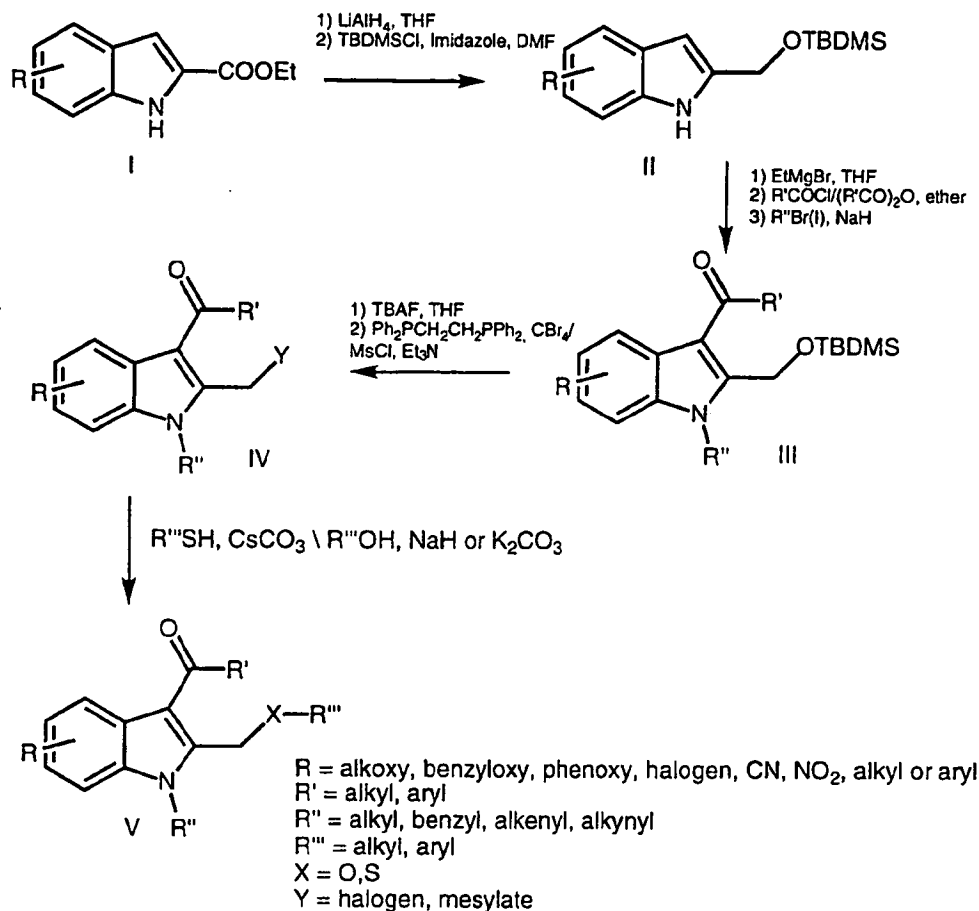
## Method G



$R$  = alkoxy, benzyloxy, phenoxy, halogen,  $\text{CN}$ ,  $\text{NO}_2$ , alkyl or aryl

$R'$  = alkyl, aryl

## Method H

**EXAMPLE 88**

**4-[(5-[(E)-[5-(benzyloxy)-1-(4-[[3,5-bis(trifluoromethyl)phenoxy]methyl]benzyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)methyl]benzoic acid**

Step 1 - The aldehyde from Example 124, (5.2 g) was suspended in ethanol (150 mL). To the thick slurry was added 2,4-thiazolidinedione (1.28g) and potassium carbonate (6.1g). The

mixture was heated in a bath at 60 °C (later dropped to 45 °C). After 1 h TLC showed no reaction. Sodium hydroxide (2.1 g) was added and the mixture was heated at 58 °C. After 45 minutes the TLC showed reaction progress. Additional 2,4-thiazolidinedione (0.1 g) was added. The mixture was stirred overnight at room temperature. The mixture was poured into water (500 mL) and acidified to pH 2 with 6 N HCl, extracted with ethyl acetate, dried (MgSO<sub>4</sub>) and filtered. Trituration from ethanol afforded an orange solid which was filtered and washed with ethanol to give the desired product (5.74 g, 94%) as an orange solid.

Step 2 - To the material prepared in step 1 (1.1 g) in DMF (15 mL) at 0 °C was added sodium hydride (0.08 g, 60% dispersion in mineral oil). The suspension was stirred for 30 minutes. To the reaction mixture was added the benzyl bromide (0.54 g) and the reaction was stirred overnight. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were concentrated. Column chromatography (1:6 ethyl acetate:hexane to 1:4 ethyl acetate:hexane) afforded the desired product (1.18 g, 75%) as a yellow solid.

Step 3 - To the material prepared in step 2 (0.34 g) in acetonitrile (15 mL) was added HF (48% aqueous, 3.7 mL) via syringe. The reaction was stirred overnight. The reaction was not complete by TLC therefore THF was added to dissolve the starting material and additional HF (0.6 mL) was added. The reaction was stirred for 2 h after which the TLC showed reaction completion. Water was added which resulted in the formation of a yellow solid. The yellow solid was dissolved in ethyl acetate, washed with brine, dried over MgSO<sub>4</sub> and concentrated. The resulting crude solid was suspended in ethanol and stirred for 30 min, filtered and dried to afford the title compound (140 mg, 48%) as a yellow solid.

#### **EXAMPLE 89**

#### **5-[(E)-(5-(benzyloxy)-1-{3-[3,5-bis(trifluoromethyl)phenoxy]propyl}-1H-indol-2-yl)methylidene]-1,3-thiazolane-2,4-dione**

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

#### **EXAMPLE 90**

5-((E)-[5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]methylidene)-1,3-thiazolane-2,4-dione

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

**EXAMPLE 91**

5-((E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene)-1,3-thiazolane-2,4-dione

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

**EXAMPLE 92**

5-((E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene)-1,3-thiazolane-2,4-dione

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

**EXAMPLE 93**

5-((E)-[1-(4-benzylbenzyl)-5-(benzyloxy)-1H-indol-2-yl]methylidene)-1,3-thiazolane-2,4-dione

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

**EXAMPLE 94**

5-((E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene)-1,3-thiazolane-2,4-dione

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

**EXAMPLE 95**

5-((E)-[5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]methylidene)-1,3-thiazolane-2,4-dione

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

**EXAMPLE 96**

**2-(5-{(E)-[5-(benzyloxy)-1-(4-{[3,5-bis(trifluoromethyl)phenoxy]methyl}benzyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)acetic acid**

Step 1 - The desired intermediate was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

Step 2 - The desired intermediate was prepared from the above intermediate as illustrated in Example 88, step 2, using the appropriate alkylating agent.

Step 3 - The title compound was prepared from the above intermediate as illustrated in Example 88, step 3.

**EXAMPLE 97**

**4-[(5-{(E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)methyl]benzoic acid**

Step 1 - The desired intermediate was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

Step 2 - The desired intermediate was prepared from the above intermediate as illustrated in Example 88, step 2, using the appropriate alkylating agent.

Step 3 - The title compound was prepared from the above intermediate as illustrated in Example 88, step 3.

**EXAMPLE 98**

**2-(5-{(E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)acetic acid**

Step 1 - The desired intermediate was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

Step 2 - The desired intermediate was prepared from the above intermediate as illustrated in Example 88, step 2, using the appropriate alkylating agent.

Step 3 - The title compound was prepared from the above intermediate as illustrated in Example 88, step 3.

#### **EXAMPLE 99**

##### **4-[(5-{(E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)methyl]benzoic acid**

Step 1 - The desired intermediate was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

Step 2 - The desired intermediate was prepared from the above intermediate as illustrated in Example 88, step 2, using the appropriate alkylating agent.

Step 3 - The title compound was prepared from the above intermediate as illustrated in Example 88, step 3.

#### **EXAMPLE 100**

##### **2-(5-{(E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)acetic acid**

Step 1 - The desired intermediate was prepared as illustrated in Example 88, step 1, starting with the appropriate indole.

Step 2 - The desired intermediate was prepared from the above intermediate as illustrated in Example 88, step 2, using the appropriate alkylating agent.

Step 3 - The title compound was prepared from the above intermediate as illustrated in Example 88, step 3.

The compounds of the following Examples 101-106 were prepared as illustrated in Example 88, step 1, starting with the appropriate indole and rhodanine.

**EXAMPLE 101**

5-((E)-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl}methylidene)-2-thioxo-1,3-thiazolan-4-one

**EXAMPLE 102**

5-((E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one

**EXAMPLE 103**

5-[(E)-(5-(benzyloxy)-1-{3-[3,5-bis(trifluoromethyl)phenoxy]propyl}-1H-indol-2-yl)methylidene]-2-thioxo-1,3-thiazolan-4-one

**EXAMPLE 104**

5-((E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one

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**EXAMPLE 105**

5-((E)-[1-(4-benzylbenzyl)-5-(benzyloxy)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one

**EXAMPLE 106**

5-((E)-[5-(benzyloxy)-1-(4-{[3,5-bis(trifluoromethyl)phenoxy]methyl}benzyl)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one

**EXAMPLE 107**

4-[[5-((E)-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl}methylidene)-4-oxo-2-thioxo-1,3-thiazolan-3-yl]methyl]benzoic acid



Step 1 - The desired intermediate was prepared as illustrated in Example 88, step 1, starting with the appropriate indole and rhodanine.

Step 2 - The desired intermediate was prepared from the above intermediate as illustrated in Example 88, step 2, using the appropriate alkylating agent.

Step 3 - The title compound was prepared from the above intermediate as illustrated in Example 88, step 3.

#### **EXAMPLE 108**

##### **5-((E)-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl)methylidene}-2-thioxotetrahydro-4H-imidazol-4-one**

The title compound was prepared as illustrated in Example 88, step 1, starting with the appropriate indole and 2-thiohydantoin

#### **EXAMPLE 109**

##### **1-benzyl-5-(2-thienyl)-1H-indole-2-carboxylic acid**

To a sealed tube containing 2-[5-bromo-1-benzyl-1H-indole-2-carboxylic acid (100 mg, 0.303 mmol) and 2-thiopheneboronic acid (116 mg, 0.909 mmol), (C<sub>6</sub>H<sub>5</sub>)<sub>4</sub>Pd (42 mg, 0.036 mmol), Na<sub>2</sub>CO<sub>3</sub> (2.42 mmol) in a mixture of benzene-ethanol-H<sub>2</sub>O (5/1/2=v/v, 4.5 mL) was heated at 100 °C for 23 h. The mixture was poured onto diethyl ether and adjusted to pH 3 before extracting with diethyl ether. The organic layer was washed with NaH<sub>2</sub>PO<sub>4</sub>, dried over MgSO<sub>4</sub> and evaporated to give the crude product which was purified on silica gel column (15% EtOAc in hexane with 1% HCOOH) to give 65 mg of the product.

#### **EXAMPLE 110**

##### **5-(1-benzofuran-2-yl)-1-benzyl-1H-indole-2-carboxylic acid**

The title compound was prepared according to the procedure described in Example 109 except that benzo[b]fran-2-boronic acid was used.

#### **EXAMPLE 111**

##### **1-benzyl-5-(4-fluorophenyl)-1H-indole-2-carboxylic acid**

The title compound was prepared according to the procedure described in Example 109 except that 4-fluorophenylboronic acid was used.

**EXAMPLE 112****1-benzyl-5-(3-methoxyphenyl)-1H-indole-2-carboxylic acid**

The title compound was prepared according to the procedure described in Example 109 except that 3-methoxyphenylboronic acid was used.

**EXAMPLE 113****1-benzyl-5-phenyl-1H-indole-2-carboxylic acid**

The title compound was prepared according to the procedure described in Example 109 except that phenylboronic acid was used.

**EXAMPLE 114****1-benzhydryl-5-bromo-1H-indole-2-carboxylic acid**

To 5-bromoindole-2-carboxylic acid (1.024 g, 4.26 mmol) in 1-methyl-2-pyrrolidinone (13 mL) at 0 °C were added  $i\text{Pr}_2\text{NEt}$  (25.6 mmol), tetrabutylammonium iodide (157 mg, 0.426 mmol) and bromodiphenylmethane (1.20 g, 4.86 mmol). The reaction mixture was heated at 50 °C for 21 h before partitioning between diethyl ether and ice water. After adjusting the pH to 3, the aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with  $\text{NaH}_2\text{PO}_4$ , dried over  $\text{MgSO}_4$  and evaporated to dryness. Purification on silica gel column ( 15% EtOAc in hexane) yielded 1.51 g (87 % yield) of the product.

**EXAMPLE 115****5-[3-(acetylamino)phenyl]-1-benzhydryl-1H-indole-2-carboxylic acid**

The title compound was prepared according to the procedure described in Example 109 except that 3-acetamidobenzeneboronic acid and 1-benzhydryl-5-bromo-1H-indole-2-carboxylic acid were used.

**EXAMPLE 116****1-benzhydryl-5-(2-thienyl)-1H-indole-2-carboxylic acid**

The title compound was prepared according to the procedure described in Example 109 except that 1-benzhydryl-5-bromo-1H-indole-2-carboxylic acid and 2-thiopheneboronic acid were used.

#### **EXAMPLE 117A**

##### **5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indole-2-carboxylic acid**

###### **Step 1**

To an ice-cold (0°C) solution of 2-ethoxycarbonyl-5-benzyloxyindole (5.0g, 16.9mmol) in dimethylformamide (50ml) was added sodium hydride (0.62g, 18.6mmol). The ice bath was removed after 10min and the reaction was stirred at rt for an addition 30min at which time bis(trifluoromethyl)benzyl bromide (3.8ml, 20.3mmol) was added dropwise. The green mixture was stirred at rt for 4h, water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated. The product was recrystallized from EtOAc/Hex to afford 6.87g (81%) of the desired intermediate as an off-white powder.

###### **Step 2**

To a solution of the above intermediate (1.3g, 2.5mmol) in THF (50ml) was added 1N NaOH (5ml) and MeOH (6ml). The mixture was stirred overnight at rt and then concentrated. The residue was suspended in water and acidified with HOAc. The product was extracted with EtOAc, the combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated to afford a quantitative yield of the title compound as an off-white solid.

#### **EXAMPLE 117B**

##### **5-[(5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl)carbonyl)amino]-2-[(5-chloro-3-pyridinyl)oxy]benzoic acid**

###### **Step 1**

To a solution of the title compound above (0.4g, 0.8mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5ml) and a few drops of DMF was added oxalyl chloride (0.2ml, 2.4mmol). The reaction was stirred for 1.5h and concentrated. The resulting yellow residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2ml) and added to a solution of the pyridyl aminobenzoate ether (0.24g, 0.8mmol) and pyridine (0.1ml, 0.9mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8ml). The reaction was stirred overnight at rt, water was added and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with saturated aqueous NH<sub>4</sub>Cl, water,

brine and dried over  $\text{MgSO}_4$ . Concentration and flash chromatography (Hex/EtOAc, 3/2) afforded 0.182g (51%) of the desired intermediate as a tan solid.

#### Step 2

To a solution of the above intermediate (0.136g, 0.2mmol) in THF (3ml), was added LiOH (0.022g, 0.5mmol) and water (0.5ml). The mixture was stirred overnight at rt, concentrated and the resulting residue was suspended in water and acidified with HOAc. The product was extracted with EtOAc, the combined organic layers were washed with water, brine and dried over  $\text{MgSO}_4$ . Concentration gave 0.122g of the title compound (94%) as a white crystalline solid.

#### **EXAMPLE 117C**

##### **5-(benzyloxy)-1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indole-2-carboxylic acid**

The procedure in EXAMPLE 117A steps 1 and 2 were followed using 2-ethoxycarbonyl-5-benzyloxyindole (2.0g, 3.2mmol) and the appropriate alkylating reagent to afford 1.7g (41% for 2 steps) of the title compound as a yellow solid.

#### **EXAMPLE 117D**

##### **5-(benzyloxy)-1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indole-2-carboxylic acid**

The procedure in EXAMPLE 117A steps 1 and 2 were followed using 2-ethoxycarbonyl-5-benzyloxyindole (2.0g, 3.2mmol) and the appropriate alkylating reagent to afford 1.7g (41% for 2 steps) of the title compound as a yellow solid.

#### **EXAMPLE 118**

##### **5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-2-(1H-1,2,3,4-tetraazol-5-yl)-1H-indole**

#### Step 1

To a suspension of the acid prepared in Example 117A (1.5g, 3.0mmol) in  $\text{CH}_2\text{Cl}_2$  (20ml) was added oxalyl chloride (0.8ml, 9.1mmol) and three drops of DMF. The mixture became homogeneous and was stirred for 1h at rt. The reaction was concentrated and redissolved in  $\text{CH}_2\text{Cl}_2$  (5ml) and  $\text{NH}_4\text{OH}$  (2.0ml) was added. The biphasic mixture was stirred for 24h and concentrated. The remaining aqueous residue was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined

organic layers washed with brine, dried and concentrated to give 1.4g (95%) of the desired intermediate as a yellow powder.

### Step 2

To an ice-cold solution of DMF (0.23 ml, 3.0mmol) in CH<sub>3</sub>CN (10ml) was added oxalyl chloride (0.24ml, 0.28mmol). A white precipitate formed immediately and the solution was stirred for an additional 5 min. A solution of the above intermediate (1.2g, 2.5mmol) in CH<sub>3</sub>CN (5ml) was added. The resulting yellow-orange solution was stirred for 10 min and pyridine (0.44ml, 5.5mmol) was added. After 5 min the red mixture was partitioned between 10% aqueous HCl and EtOAc. The organic layer was dried and concentrated to give 1.0g (84%) of the desired intermediate as a yellow powder.

### Step 3

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5-(benzyloxy)-1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indole-2-carboxylic acid

To a solution of the above intermediate (0.94g, 2.0mmol) in N-methyl-2-pyrrolidinone (10ml) was added sodium azide (0.39g, 5.9mmol). The mixture was heated at reflux for 2h. The reaction was allowed to cool to rt and poured into 50ml of ice water. The resulting solution was adjusted to pH=2 with 10% aqueous HCl and a tan precipitate formed. The mixture was filtered and washed with EtOAc. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 10:1) gave 0.78g (78%) of the title compound as a white powder.

### EXAMPLE 119

benzyl 1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-2-(1H-1,2,3,4-tetraazol-5-yl)-1H-indol-5-yl ether acid was prepared in an analogous manner to Example 118 according to steps 1-3 starting from the acid prepared in EXAMPLE 117C.

### EXAMPLE 120

4-([5-((E)-5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl)methylidene)-4-oxo-2-thioxo-1,3-thiazolan-3-yl]methyl}benzoic acid

**Step 1**

The thiasolidinedione prepared in Example 101 (0.1g, 0.2mmol), was alkylated by treatment with sodium hydride (0.006g, 0.22mmol), and the bromomethyl SEM ester (0.058g, 0.2mmol) in DMF (2ml). Flash chromatography (Hex/EtOAc, 4/1) gave 0.073g (50%) of the desired intermediate as a thick oil.

**Step 2**

To a solution of the above intermediate (0.07g, 0.1mmol) in CH<sub>3</sub>CN (5ml) was added aqueous 48% HF (2ml). After 2h water was added and the product was extracted with EtOAc, the combined organic layers were washed with water, brine and dried over MgSO<sub>4</sub>. Concentration gave 0.025g of the title compound (42%) as an orange powder.

**Example 121**

**5-((Z,2E)-3-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl}-2-propenylidene)-1,3-thiazolane-2,4-dione**

**Step 1**

A solution of the intermediate prepared in EXAMPLE 117A, step 1 (4.4g, 8.4mmol) in THF (30ml) was cooled to 0°C and a solution of lithium aluminum hydride in THF (1.0M, 8.4ml) was added dropwise with vigorous stirring. After 1h at 0°C the reaction was carefully quenched with a saturated solution of NH<sub>4</sub>Cl. The salts were filtered and washed with EtOAc. Concentration of the solvents afforded 3.9g (96%) of the alcohol as a yellow foam. The alcohol (1.6g, 3.3mmol) was dissolved in THF (50ml) and MnO<sub>2</sub> (2.91g, 33.4mmol) was added. The reaction was stirred for 12h and filtered through a pad of Celite. Concentration of the filtrate gave 1.47g (92%) of the desired intermediate as a thick clear oil.

**Step 2**

To an ice-cold solution of trimethylphosphonoacetate (0.5ml, 3.1mmol) in DMF (10ml) was added sodium hydride (0.14g, 3.4mmol) and the reaction was stirred for 20min. A solution of the above intermediate (1.47g, 3.1mmol) in DMF (3ml) was added, the ice bath was removed and the reaction was allowed to stir overnight at rt. Water was added and the aqueous phase was extracted with EtOAc. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated. Flash chromatography (Hex/EtOAc, 3/2) provided 1.5g (93%) of the desired intermediate as a yellow solid.

**Step 3**

The above intermediate (0.5g, 0.9mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (10ml) and the solution was cooled to  $-20^\circ\text{C}$ . A solution of diisobutylaluminium hydride (1.0M in toluene, 1.9ml) was added dropwise, and the reaction was allowed to stir at rt overnight. Water was added, and the mixture was filtered through a pad of celite. The filtrate was diluted with EtOAc, washed with water and the combined organic layers washed with brine, dried and concentrated. Flash chromatography (Hex/EtOAc, 3/2) gave 0.49g (75%) of an orange solid. This material was dissolved in THF (12ml) and  $\text{MnO}_2$  (1.1g, 12.3mmol) was added. The mixture was stirred overnight and filtered through a pad of Celite. Concentration of the solvent afforded 0.4g (65%) of the desired intermediate as a thick tan oil.

**Step 4**

The above intermediate (0.1g, 0.2mmol) was dissolved in toluene (1ml), followed by piperidine (6 $\mu\text{l}$ , 0.1mmol) acetic acid (1.2 $\mu\text{l}$ ) and 2,4-thiazolidinedione (0.023g, 0.2mmol). The mixture was heated to reflux for 2h. The reaction was allowed to cool to rt, water was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried and concentrated. Flash chromatography (Hex/EtOAc, 3/2) gave 0.056g (47%) of the title compound as a red powder.

**EXAMPLE 122****5-(benzyloxy)-1-(4-{[3,5-bis(trifluoromethyl)phenoxy]methyl}benzyl)-1H-indole-2-carboxylic acid**

**Step 1:** To ethyl 5-benzyloxy-2-indolcarboxylate (1 g, 3.4 mmol) in 12 ml of DMF, sodium hydride (0.163g, 60% oil dispersion, 4.07 mmol) is added at room temperature. The reaction is stirred for 30 minutes. a-Bromo-a'-[3,5-bis(trifluoromethyl)phenoxy]p-xylene (1.54 g, 3.73 mmol) is added at this time and the reaction stirred overnight. On completion of the reaction (monitored by TLC) it is quenched with water, extracted with ethyl acetate (3X). Organic layers are dried over magnesium sulfate, concentrated and used for the next step.

**Step 2:** The ester ( 2.1 g, 3.39 mmol) is dissolved in 40 mL of 1/1 THF/ methanol and then 1N sodium hydroxide (15 mL) is added and the resulting mixture is stirred for 16 hours at RT, workup gave crude product that is purified via chromatography (1:1 Hexane:Ethyl acetate with 1% acetic acid) to yield (1.73 g, 85%) of solid.

**EXAMPLE 123****5-([1-benzyl-5-(benzyloxy)-1H-indol-2-yl]carbonyl)amino)isophthalic acid**

Step 1: This intermediate was prepared according to the procedure described in Example 122, but using benzyl bromide.

Step 2: The acid (0.27 g, 0.75 mmol) prepared in step 1, EDCI (0.18 g, 0.97 mmol), DMAP (3 mg, 0.02 mmol) and dimethyl-5 aminoisophthalate (0.18g, 0.75 mmol) were dissolved in THF (8.8 mL) and refluxed for 16 hours, after workup and purification (Hexane:Ethyl Acetate 3:1) yielded (0.25 g, 60%) of pure product.

Step 3: The title compound was prepared from ester, prepared in step 2 above, according to the procedure described in step 2, Example 122.

**EXAMPLE 124****(E)-3-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]-2-propenoic acid**

Step 1: Ethyl 5-benzyloxy-2-indolcarboxylate (30 g, 102 mmol) is dissolved in 250 mL of THF and cooled to 0° C and Lithium Aluminum Hydride (LAH) (255 mL of a 1.0 M solution in THF) is added via addition funnel over 40 minutes. The reaction was stirred a further 2 hours at 0° C and then worked up by the addition of 4N NaOH (190 mL). The resulting salts are filtered and washed with ethyl acetate (3X400 mL), the filtrates are combined and dried over MgSO<sub>4</sub> and concentrated to yield 24.8 g (96%).

Step 2: Indole alcohol (26.1 g, 103 mmol) from step 1 is dissolved in THF (900 ml). Manganese dioxide (106.6 g) is added and the mixture is stirred for 2h at room temperature. After the reaction is complete the mixture is filtered through celite and washed with ethyl acetate. The filtrate is concentrated under reduced pressure, dried to give the desired aldehyde (22.9 g, 89%).

Step 3: This intermediate was prepared from indole, prepared in step 2 above and 2-(bromomethyl)naphthalene, according to the procedure described in step 1, Example 122.

Step 4: To sodium hydride (0.025 g, 60% oil dispersion, 0.63 mmol) in 7.5 mL of THF is added trimethyl phosphonoacetate (0.1 mL, 0.62 mmol) in 2.5 mL of THF at room temperature. The reaction is stirred for 10 minutes. Next the aldehyde (0.24 g, 0.62 mmol) prepared in step 3 above in 2.5 mL THF is added dropwise at room temperature. Reaction is stirred for another 30 minutes



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**EXAMPLE 133****2-([3-acetyl-1-[4-(1,3-benzothiazol-2-yl)carbonyl]benzyl]-5-(benzyloxy)-1H-indol-2-yl)methyl)sulfanyl)acetic acid**

Step 1 p-Toluoyl chloride (0.8 M) was added to triethylamine (2.44 eq) and methoxymethyl amine HCl (1.1 eq) dissolved in methylene chloride at 0°C over 20 min. The reaction was allowed to warm to 25°C. After stirring at 25°C for 1 day, workup with methylene chloride and water afforded crude product in ca. 100% yield.

Step 2 Under anhydrous conditions benzothiazole was dissolved in THF (0.35 M). At -78 °C added BuLi (1.1 eq). After 1 h at -78°C, added the amide from step 1 in THF, over 15 min. The reaction was allowed to warm to 25°C. After stirring at 25°C for 1 day, workup with ethyl acetate and water and chromatography afforded pure tolyl ketone product (52%).

Step 3 The tolyl ketone from step 2 was dissolved in carbon tetrachloride (0.19M), and NBS (1.2 eq) and AIBN (0.11 eq) were added. After 1 d at 60°C, about 1:1 of starting material and product were present. Resubmission under the same conditions, followed by filtration and recrystallization from ethyl acetate afforded pure bromobenzyl ketone product (28%).

Step 4 The intermediate from step 3, Example 131 was dissolved in dry DMF (0.1 M), followed by NaH (1.2 eq). After 1.5 h at 25°C, added the bromobenzyl ketone from step 3 and stirred for 1 d at 25°C. Workup (ethyl acetate/hexanes) and trituration (ethyl acetate/hexanes) afforded the product in 46% yield.

Step 5: The product from step 4 was dissolved in methylene chloride and 1 N HCl (ca. 0.04 M) and stirred at 25°C for 1 h. Workup (sodium bicarbonate), and trituration with ether afforded the product alcohol (89%).

Step 6: The alcohol from step 5 was dissolved in dry methylene chloride (0.014 M), treated with thionyl chloride (1.2 eq) and stirred at 25°C for 1 d. Concentration and trituration with ethyl acetate/hexanes afforded the product chloride (100%).

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Activity data for the compounds of Examples 88-135 are reported in Table VIII (assay described in Example 136) and Table IX (assay of Example 137).

### Example 136

#### Activity Assays

##### (a) Vesicle Assay

1-palmitoyl-2-[<sup>14</sup>C] arachidonyl phosphatidylcholine (58 mCi/mmol) (final concentration 6  $\mu$ M) and 1,2-dioleoylglycerol (final concentration 3  $\mu$ M) were mixed and dried under a stream of nitrogen. To the lipids was added 50 mM Hepes pH 7.5 (2x final concentration of lipids) and the suspension was sonicated for 3 min. at 4°C. To the suspension was added 50 mM Hepes pH 7.5, 300 mM NaCl, 2 mM DTT, 2 mM CaCl<sub>2</sub> and 2 mg/ml bovine serum albumin (BSA) (Sigma A7511) (1.2x final concentration of lipids). A typical assay consisted of the lipid mixture (85  $\mu$ l) to which was added consecutively, the inhibitor (5  $\mu$ l in DMSO) and cPLA<sub>2</sub>, 10 ng for an automated system or 1 ng for a manual assay, in 10  $\mu$ l of the BSA buffer. This assay was conducted by either the manual assay or automated assay protocol described below.

##### (b) Soluble Substrate Assay (LysoPC)

1-[<sup>14</sup>C]-palmitoyl-2-hydroxyphosphatidyl-choline (57 mCi/mmol) (final concentration 4.4  $\mu$ M) was dried under a stream of nitrogen. The lipid was resuspended by vortexing 80 mM Hepes pH 7.5, 1 mM EDTA (1.2 x final concentration). A typical assay consisted of lipid suspension (85  $\mu$ l) to which was added consecutively the inhibitor (5  $\mu$ l in DMSO) and cPLA<sub>2</sub>, 200 ng in 80 mM Hepes pH 7.5, 2 mM DTT and 1 M EDTA. This assay was conducted by either the manual assay or automated assay protocol described below.

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(f) RBL Assay

RBL-2H3 cells were routinely cultured at 37°C in a 5% CO<sub>2</sub> atmosphere in minimal essential medium containing nonessential amino acids and 12% fetal calf serum. The day before the experiment, cells were seeded into spinner flasks at 3 x 10<sup>6</sup> cells/ml and 100 ng/ml DNP specific-IgE was added. After 20 hrs, the cells were harvested by centrifugation and washed once in serum-free minimal essential media, and resuspended to 2 x 10<sup>6</sup> cells/ml in serum free media. The cells were then preincubated with either inhibitor in DMSO (1% v/v) or DMSO (1% v/v) for 15 min at 37°C followed by stimulation with DNP-BSA (300 ng/ml). After 6 min, the cells were removed by centrifugation, and the supernatant was assayed for PGD<sub>2</sub> content in accordance with known methods.

(g) Coumarine Assay

7-hydroxycoumarinyl 6-heptenoate was used as a monomeric substrate for cPLA<sub>2</sub> as reported previously (Huang, Z. et al., 1994, Analytical Biochemistry 222, 110-115). Inhibitors were mixed with 200µL assay buffer (80mM Hepes, pH 7.5, 1 mM EDTA) containing 60 µM 7-hydroxycoumarinyl 6-heptenoate. The reaction was initiated by adding 4 µg cPLA<sub>2</sub> in 50µL assay buffer. Hydrolysis of the 7-hydroxycoumarinyl 6-heptenoate ester was monitored in a fluorometer by exciting at 360 nm and monitoring emission at 460 nm. Enzyme activity is proportional to the increase in emission at 460 nm per minute. In the presence of a cPLA<sub>2</sub> inhibitor, the rate of increase is less.

Example 137Rat Carrageenan-Induced Footpad Edema Test

Each compound was suspended in 0.3ml absolute ethanol, 0.1 ml Tween-80 and 2.0 ml Dulbecco's PBS (without calcium or magnesium). To this mixture, 0.1ml 1N NaOH was added. After solution was complete, additional amounts of PBS were added to adjust the concentration to 1 mg/ml. All compounds remained in solution. Compounds were administered i.v. in a volume of 5 ml/kg to male Sprague Dawley rats at the same time that edema was induced by injection of 0.05ml of 1% Type IV carrageenan into the hind footpad. Footpad volume was measured before dosing with compound and 3 hours after dosing with carrageenan.

Table VIII

Example	Structure	PERCENT INHIBITION @	CONCENTRATION (micromolar)
88		68	6.25
88		50	3
89		50	22
89		50	24
89		50	37
90		50	30
90		50	23
90		50	24
90		50	28
90		50	38

Table VIII

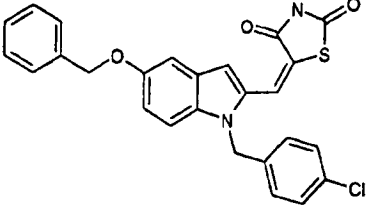
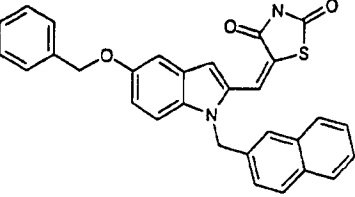
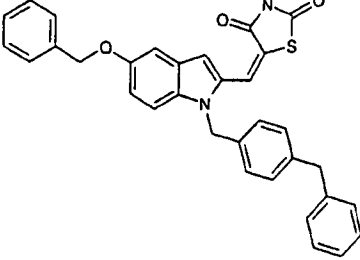
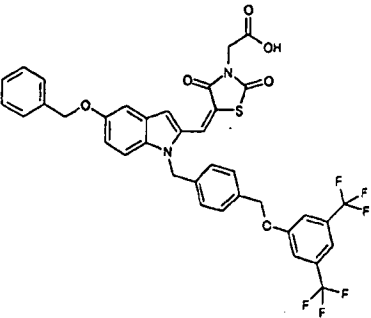
91		50	18
91		50	25
92		50	18
92		50	22
93		50	12.5
93		55	12.5
96		57	6.25
96		50	5

Table VIII

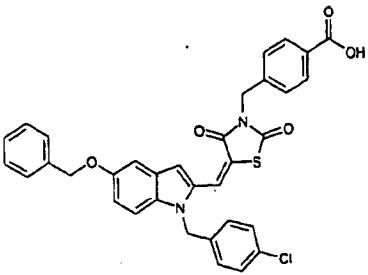
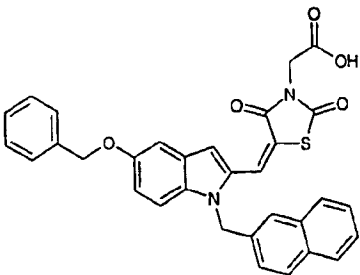
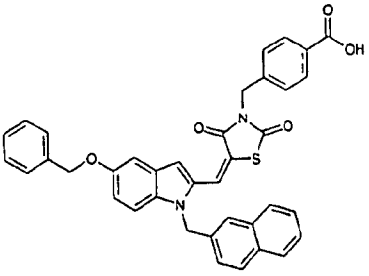
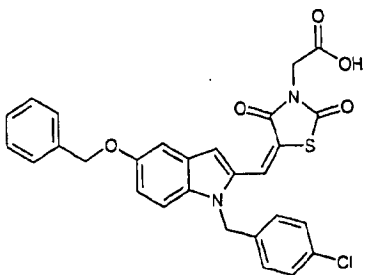
97		56	6.25
97		50	4.5
98		50	37
98		50	45
98		50	42
98		50	25
98		50	33
98		50	37
99		50	9
99		50	12
100		50	7

Table VIII

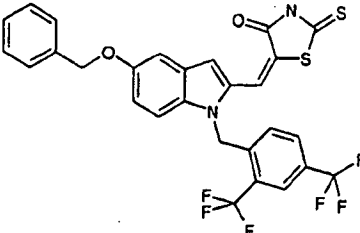
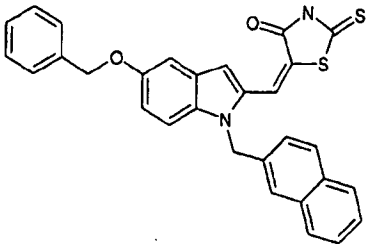
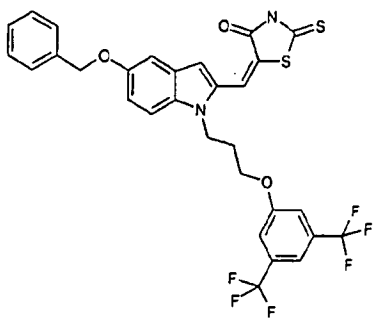
100	50	9
101	50	9.5
		
101	50	10
101	50	12.5
101	50	14
101	50	17
101	50	22
101	50	10
102	50	16
		
102	50	18
102	50	25
103	50	15
		
103	50	16
103	50	22

Table VIII

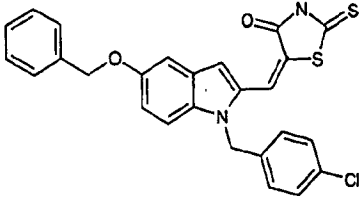
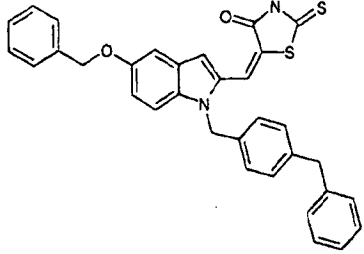
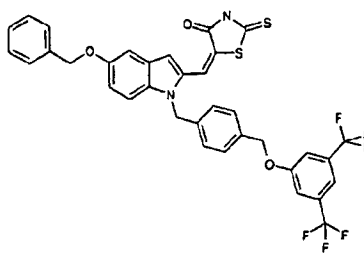
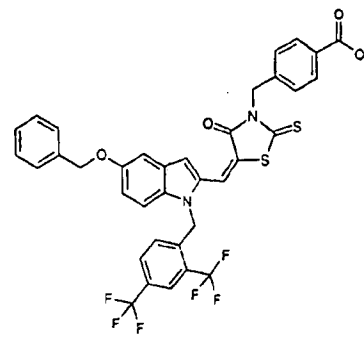
104		50	17
104		50	20
104		50	12
104		50	12
104		50	14
104		50	18
105		50	18
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106		50	9
106		50	12.5
107		50	3.8
107		67	6.2

Table VIII

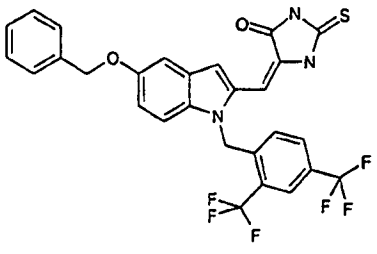
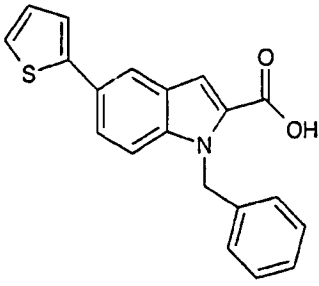
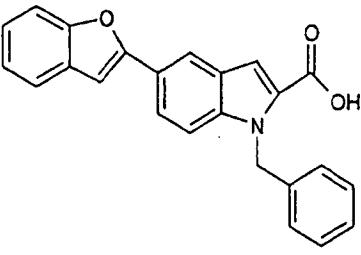
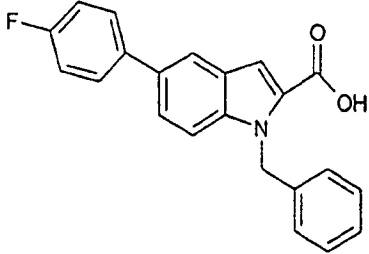
108		50	32
108		50	39
109		50	50
109		50	55
110		50	50
110		50	50
111		50	13
111		50	13

Table VIII

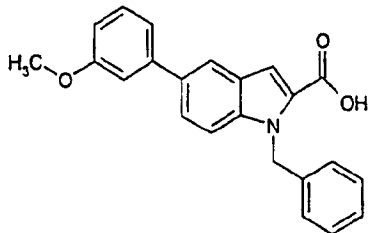
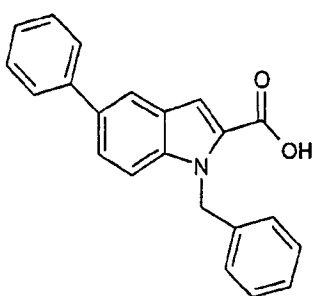
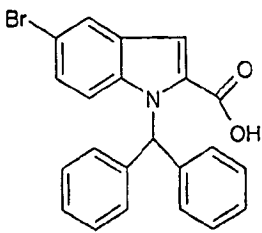
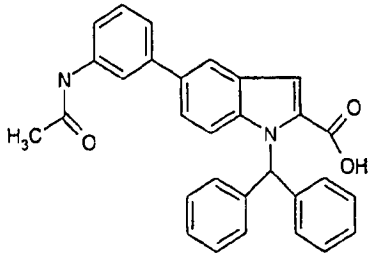
112		50	12.5
112		32	25
112		46	50
112		50	50
113		38	100
113		50	170
114		50	40
114		50	42
115		50	30
115		50	35



Table VIII

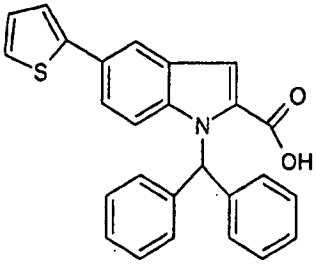
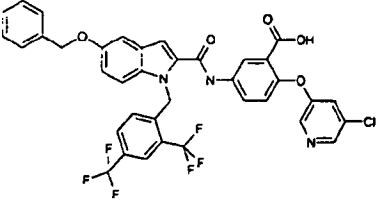
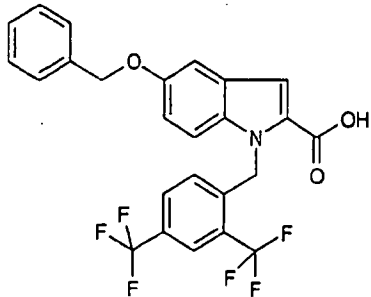
116		50	60
116		50	70
117A		50	28
117A		39	50
117B		50	34
117B		50	34
117B		50	43
117B		50	43

Table VIII

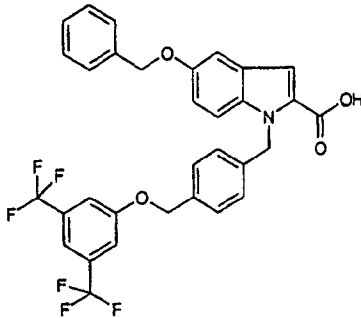
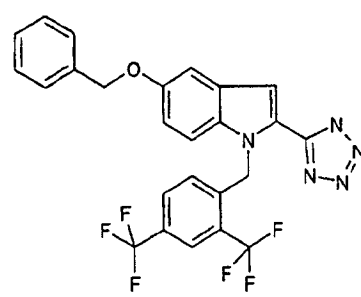
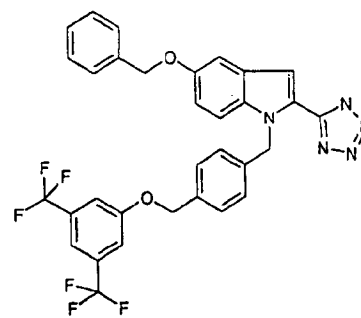
117C	50	9
		
117C	50	4
117C	50	8.5
118	50	12
		
118	50	15
119	50	5
		
119	50	4
119	50	6

Table VIII

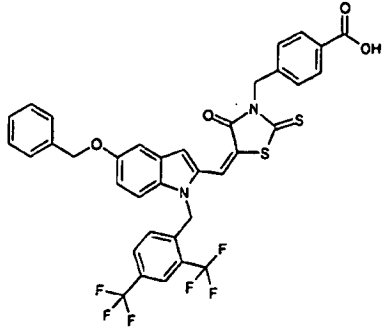
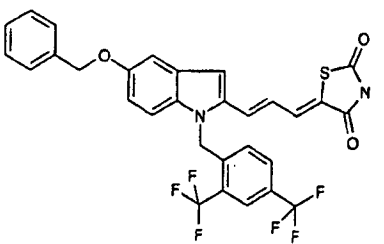
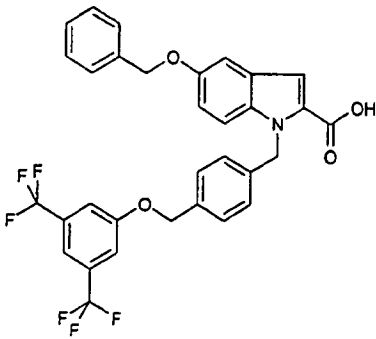
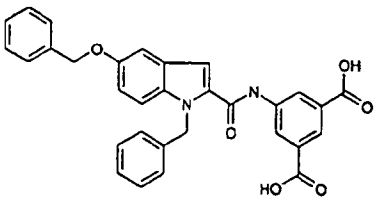
120	50i	3.8
		
120	67	6.2
120	50	3.8
120	67	6.2
	50	18.5
		
	50	20
122	50	3.75
		
122	50	10
123	31	50
		
123	25	50

Table VIII

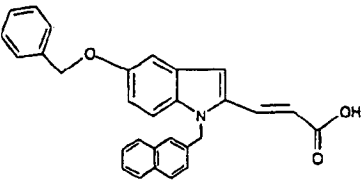
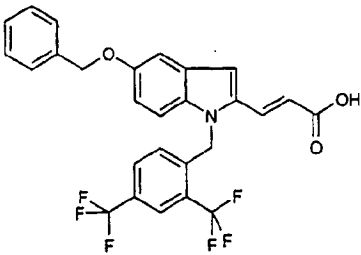
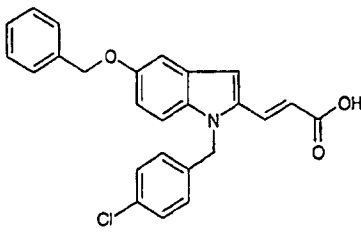
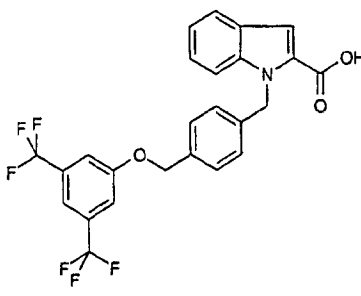
124		50	12.5
124		50	15
125		50	23
126		50	17
126		50	18
127		50	28
127		50	86

Table VIII

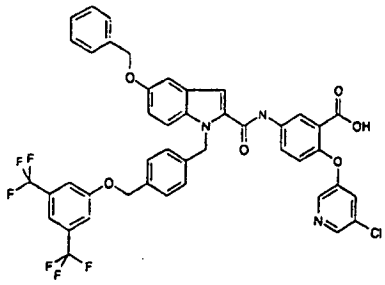
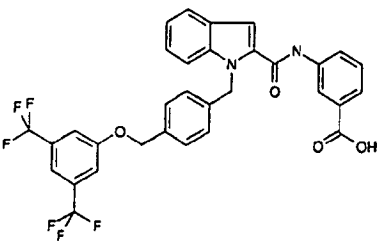
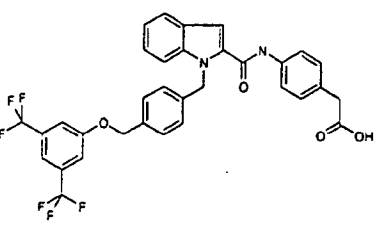
128		50	5
128		50	6
128		50	8.5
128		52	12.5
128		50	44
129		50	2.5
129			
129		50	4
129		50	3.5
129		50	3.8
129		95	12.5
129		50	30
130		50	12
130			
130		50	80
130		50	10
130		50	16
130		50	32
130		50	44
130		50	50

Table VIII

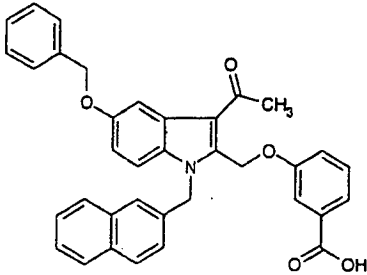
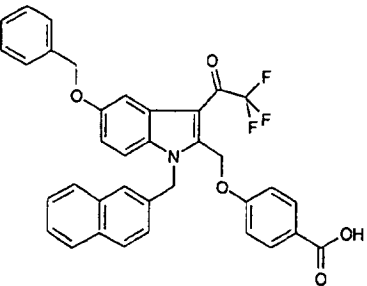
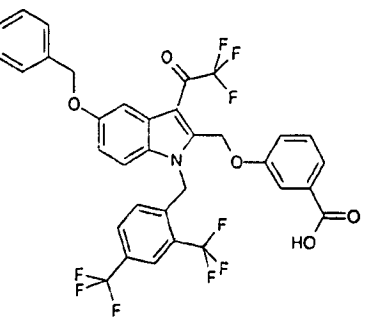
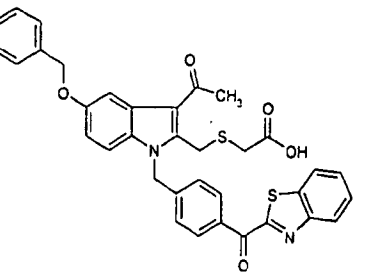
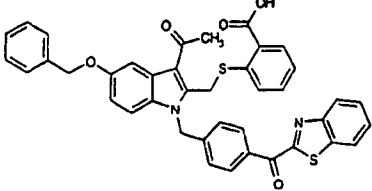
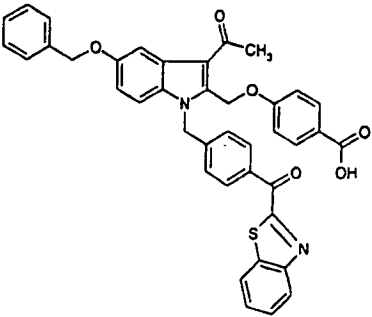
131	50	7
		
131	50	46
132A	50	9
		
132A	50	17
132A	50	30
132B	50	19
		
132B	50	20
133	50	8.5
		

Table VIII

134		50	3.5
135		50	9

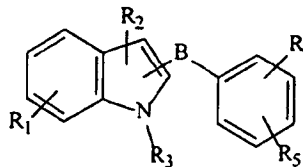
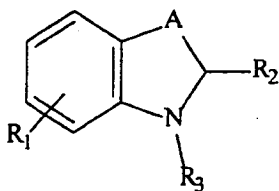
All patent and literature references cited herein are incorporated as if fully set forth herein.



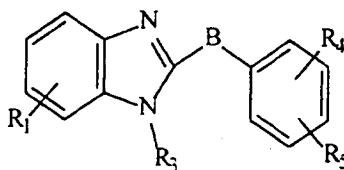
What is claimed is:

1. A compound having a chemical formula selected from the group consisting of:

;



and



or a pharmaceutically acceptable salt thereof, wherein:

A is independent of any other group and is selected from the group consisting of -CH<sub>2</sub>- and -CH<sub>2</sub>-CH<sub>2</sub>-;

B is independent of any other group and is selected from the group consisting of -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>O)<sub>n</sub>-, -(CH<sub>2</sub>S)<sub>n</sub>-, -(OCH<sub>2</sub>)<sub>n</sub>-, -(SCH<sub>2</sub>)<sub>n</sub>-, -(CH=CH)<sub>n</sub>-, -(C≡C)<sub>n</sub>-, -CON(R<sub>6</sub>)-, -N(R<sub>6</sub>)CO-, -O-, -S- and -N(R<sub>6</sub>)-;

R<sub>1</sub> is independent of any other R group and is selected from the group consisting of -X-R, -H, -OH, halogen, -CN, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>5</sub> alkyl, alkenyl, alkynyl, aryl and substituted aryl;

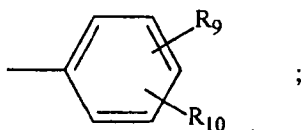
R<sub>2</sub> is independent of any other R group and is selected from the group consisting of -H, -COOH, -COR<sub>5</sub>, -CONR<sub>5</sub>R<sub>6</sub>, -(CH<sub>2</sub>)<sub>n</sub>-W-(CH<sub>2</sub>)<sub>m</sub>-Z-R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>-W-R<sub>5</sub>, -Z-R<sub>5</sub>, C<sub>1</sub>-C<sub>10</sub> alkyl, alkenyl and substituted aryl;

R<sub>3</sub> is independent of any other R group and is selected from the group consisting of -H, -COOH, -COR<sub>5</sub>, -CONR<sub>5</sub>R<sub>6</sub>, -(CH<sub>2</sub>)<sub>n</sub>-W-(CH<sub>2</sub>)<sub>m</sub>-Z-R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>-W-R<sub>5</sub>, -Z-R<sub>5</sub>, C<sub>1</sub>-C<sub>10</sub> alkyl, alkenyl and substituted aryl;

R<sub>4</sub> is independent of any other R group and is selected from the group consisting of -H, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -NHR<sub>6</sub>, -COOH, -CONR<sub>6</sub>R<sub>7</sub>, -NO<sub>2</sub>, -CONHSO<sub>2</sub>R<sub>8</sub>, C<sub>1</sub>-C<sub>5</sub> alkyl, alkenyl and substituted aryl;

R<sub>5</sub> is independent of any other R group and is selected from the group consisting of -H, -OH, -

$O(CH_2)_nR_6$ ,  $-SR_6$ ,  $-CN$ ,  $-COR_6$ ,  $-NHR_6$ ,  $-COOH$ ,  $-NO_2$ ,  $-COOH$ ,  $-CONR_6R_7$ ,  
 $-CONHSO_2R_8$ ,  $C_1-C_5$  alkyl, alkenyl, alkynyl, aryl, substituted aryl,  $-CF_3$ ,  $-CF_2CF_3$  and



$R_6$  is independent of any other R group and is selected from the group consisting of  $-H$ ,  $C_1-C_5$  alkyl, alkenyl, alkynyl, aryl and substituted aryl;

$R_7$  is independent of any other R group and is selected from the group consisting of  $-H$ ,  $C_1-C_5$  alkyl, alkenyl, alkynyl, aryl and substituted aryl;

$R_8$  is independent of any other R group and is selected from the group consisting of  $C_1-C_5$  alkyl, aryl and substituted aryl;

$R_9$  is independent of any other R group and is selected from the group consisting of  $-H$ ,  $-OH$ , a halogen,  $-CN$ ,  $-OR_6$ ,  $-COOH$ ,  $-CONR_6R_7$ , tetrazole,  $-CONHSO_2R_8$ ,  $-COR_6$ ,  $-(CH_2)_nCH(OH)R_6$  and  $-(CH_2)_nCH_2R_6R_5$ ;

$R_{10}$  is independent of any other R group and is selected from the group consisting of  $-H$ ,  $-OH$ , a halogen,  $-CN$ ,  $-OR_6$ ,  $-COOH$ ,  $-CONR_6R_7$ , tetrazole,  $-CONHSO_2R_8$ ,  $-COR_6$ ,  $-(CH_2)_nCH(OH)R_6$  and  $-(CH_2)_nCH_2R_6R_5$ ;

W is, independently each time used including within the same compound, selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-CH_2-$ ,  $-CH=CH-$ ,  $-C \equiv C-$  and  $-N(R_6)-$ ;

X is independent of any other group and is, independently each time used including within the same compound, selected from the group consisting of  $-O-$ ,  $-S-$  and  $-N(R_6)-$ ;

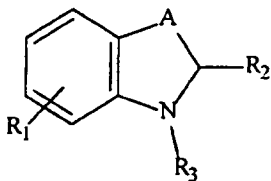
Z is independent of any other group and is, independently each time used including within the same compound, selected from the group consisting of  $-CH_2-$ ,  $-O-$ ,  $-S-$ ,  $-N(R_6)-$ ,  $-CO-$ ,  $-CON(R_6)-$  and  $-N(R_6)CO-$ ;

m is, independently each time used including within the same compound, an integer from 0 to 4; and

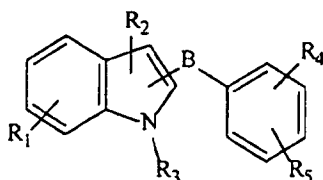
n is independent of m and is, independently each time used including within the same compound, an integer from 0 to 4.

2. The compound of claim 1 having phospholipase enzyme inhibiting activity.

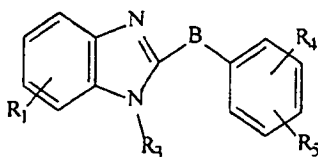
3. The compound of claim 1 wherein said compound has the following chemical formula:



4. The compound of claim 1 wherein said compound has the following chemical formula:



5. The compound of claim 1 wherein compound has the following chemical formula:

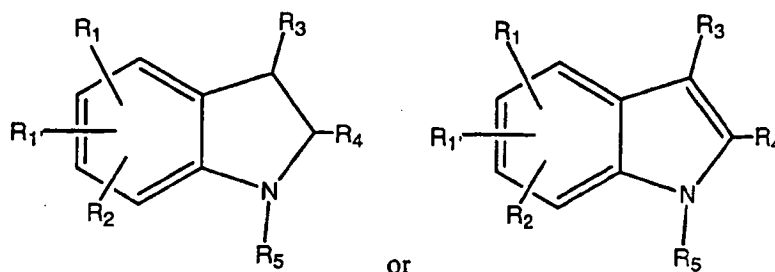


6. The compound of claim 1 wherein A is  $-\text{CH}_2-$  and  $\text{R}_2$  is  $-(\text{CH}_2)_n-\text{W}-(\text{CH}_2)_m-\text{ZR}_5$ .

7. The compound of claim 6 wherein n is 1, m is 1, W is  $-\text{S}-$  and Z is  $-\text{CO}-$ .
8. The compound of claim 7 wherein  $\text{R}_5$  is  $-\text{NHR}_6$ .
9. The compound of claim 8 wherein  $\text{R}_6$  is a substituted aryl group.

10. The compound of claim 9 wherein said aryl group is substituted with one or more substituents independently selected from the group consisting of a halogen,  $-\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_3$ ,  $-(\text{CH}_2)_p\text{COOH}$ ,  $-(\text{CH}_2)_p\text{CH}_3$ ,  $-\text{O}(\text{CH}_2)_p\text{CH}_3$ ,  $-(\text{CH}_2)_p\text{OH}$ ,  $-(\text{CH}_2)_p\text{S}(\text{C}_6\text{H}_5)$ ,  $-(\text{CH}_2)_p\text{CONH}_2$  and  $-\text{CHR}_{11}\text{COOH}$ , wherein  $\text{R}_{11}$  is selected from the group consisting of alkyl, alkenyl, alkynyl,  $-(\text{CH}_2)_p\text{OH}$ , and  $-\text{O}(\text{CH}_2)_p\text{CH}_3$ , and wherein  $p$  is an integer from 0 to 4.
11. The compound of claim 6 wherein  $\text{R}_1$  is selected from the group consisting of  $-\text{H}$  and  $-\text{OCH}_2(\text{C}_6\text{H}_5)$ .
12. The compound of claim 6 wherein  $\text{R}_3$  is  $-\text{COR}_5$ ,  $\text{R}_5$  is  $-\text{OCH}_2\text{R}_6$  and  $\text{R}_6$  is a substituted aryl group.
13. The compound of claim 12 wherein said aryl group is substituted with one or more substituents selected from the group consisting of  $-\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_3$  and  $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$ .
14. A method of inhibiting the phospholipase enzyme activity of an enzyme, comprising administering to a mammalian subject a therapeutically effective amount of a compound of claim 1.
15. A method of treating an inflammatory condition, comprising administering to a mammalian subject a therapeutically effective amount of a compound of claim 1.
16. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

17. A compound of the formula:



wherein

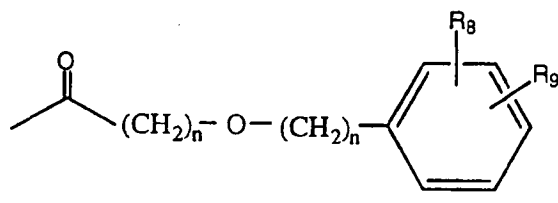
$R_1$  and  $R_2$  are independently selected from  $C_1$ - $C_6$  alkyl,  $-Z$ - $C_1$ - $C_6$  alkyl, phenyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -phenyl, benzyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -benzyl, naphthyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -naphthyl, pyrimidinyl,  $-(CH_2)_n$ - $Z$ -( $CH_2$ ) $_n$ -pyrimidinyl, the alkyl, phenyl, benzyl, naphthyl and pyrimidinyl groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ , or  $-OH$ ;

$Z$  is O or S;

$n$  is an integer from 0 to 3;

$R_3$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH$ - $C_1$ - $C_6$  alkyl,  $-N$ ( $C_1$ - $C_6$  alkyl) $_2$ ,  $-N$ - $SO_2$ - $C_1$ - $C_6$  alkyl, or  $-SO_2$ - $C_1$ - $C_6$  alkyl;

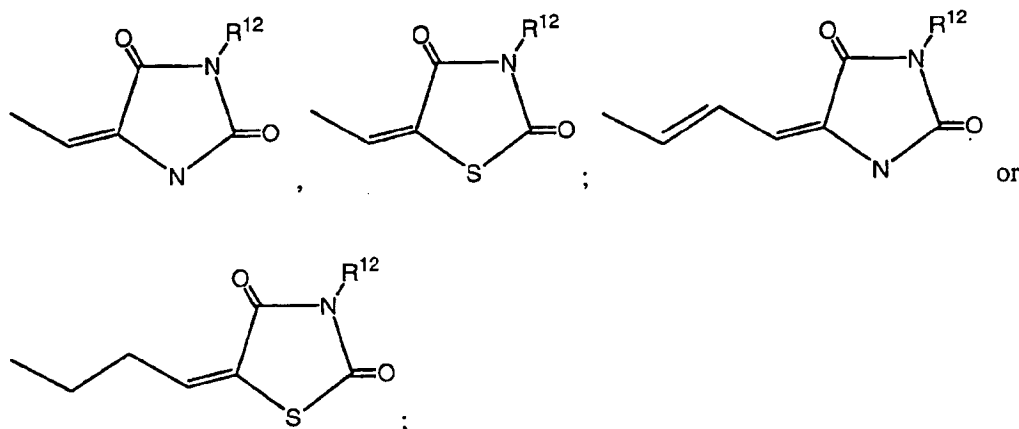
$R_4$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy,  $-CHO$ ,  $-C(O)CH_3$ ,  $-C(O)$ -( $CH_2$ ) $_n$ - $CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH$ - $C_1$ - $C_6$  alkyl,  $-N$ ( $C_1$ - $C_6$  alkyl) $_2$ ,  $-N$ - $SO_2$ - $C_1$ - $C_6$  alkyl,  $-SO_2$ - $C_1$ - $C_6$  alkyl or a moiety of the formula:



$n$  in each appearance is independently selected as an integer selected from 0-3;

$R^8$  and  $R^9$  are independently selected in each appearance from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,  $-\text{NH}(\text{C}_1-\text{C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})_2$ ;

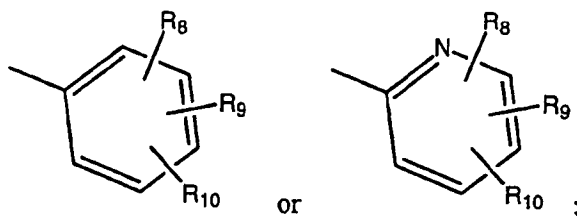
$R_4$  is selected from  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{CH}=\text{CH}-\text{COOH}$ , tetrazole,  $-(\text{CH}_2)_n$ -tetrazole, the moiety  $-\text{L}^1-\text{M}^1$  or a moiety of the formulae:



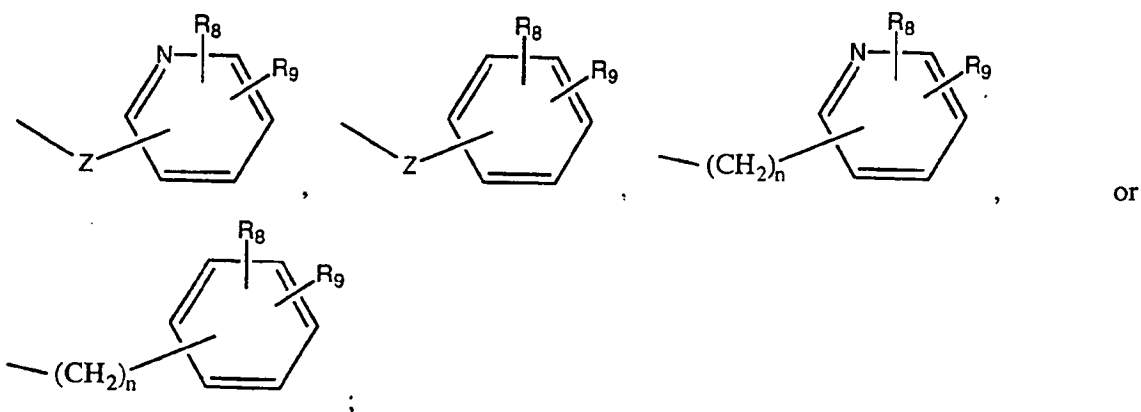
$R^{12}$  is selected from H,  $-\text{CF}_3$ ,  $\text{C}_1-\text{C}_6$  alkyl,  $-(\text{CH}_2)_n-\text{C}_3-\text{C}_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C(O)}-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,  $-\text{NH}(\text{C}_1-\text{C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})_2$ ;

$\text{L}^1$  is selected from  $-(\text{CH}_2)_n-\text{O}-$ ,  $-(\text{CH}_2)_n-\text{S}-$ ,  $-(\text{CH}_2)_n-\text{O}-(\text{CH}_2)_n-$ ,  $-(\text{CH}_2)_n-\text{S}-(\text{CH}_2)_n-$ ,  $-\text{C(O)}-\text{O}-$ ,  $-\text{C(O)}-(\text{CH}_2)_n-\text{O}-$ ,  $-\text{C(O)}-\text{N}-$ , or  $-(\text{CH}_2)_n-\text{S}-(\text{CH}_2)_n-\text{C(O)}-\text{N}-$ ;

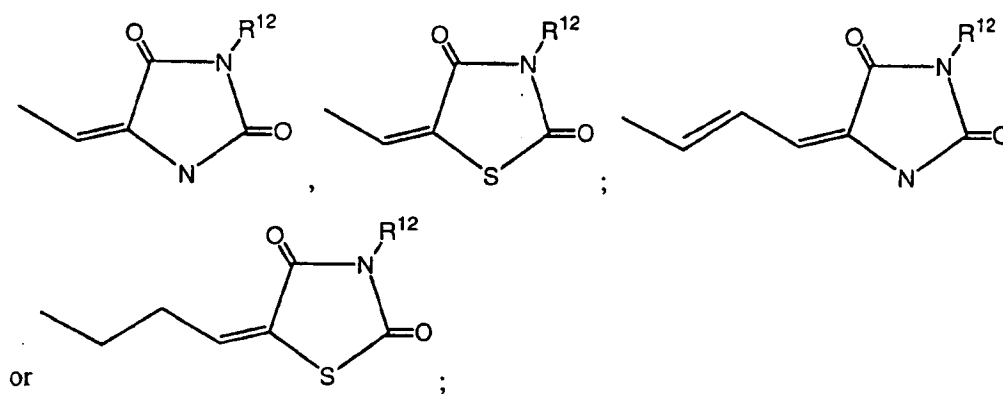
$\text{M}^1$  is  $-\text{COOH}$  or a moiety selected from:



$R^{10}$  is selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ ,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{O}-\text{C}_1-\text{C}_6$  alkyl,



with a proviso that the moiety or combination of moieties comprising  $R^3$  include an acidic group selected from carboxylic acid or a moiety of the formulae:

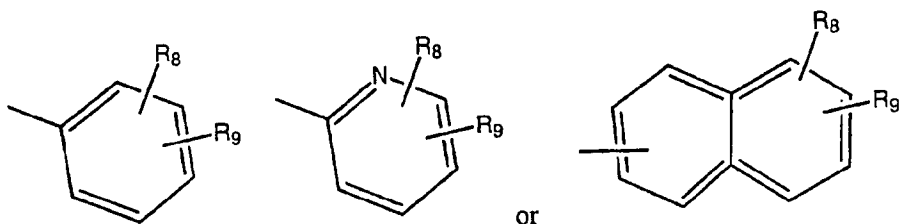


$R_5$  is selected from:

a) a moiety of the formula  $-L^2-M^2$ ;

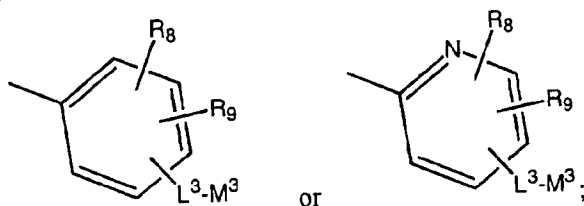
$L^2$  is selected from a chemical bond or a bridging group selected from  $-(CH_2)_n-Z-$ ,  $-(CH_2)_n-Z-(CH_2)_n-$ ,  $-C(O)-O-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

$M^2$  is selected from  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,



wherein  $R^8$  and  $R^9$  are as defined above and can be substituted anywhere on the cyclic or bicyclic ring; or

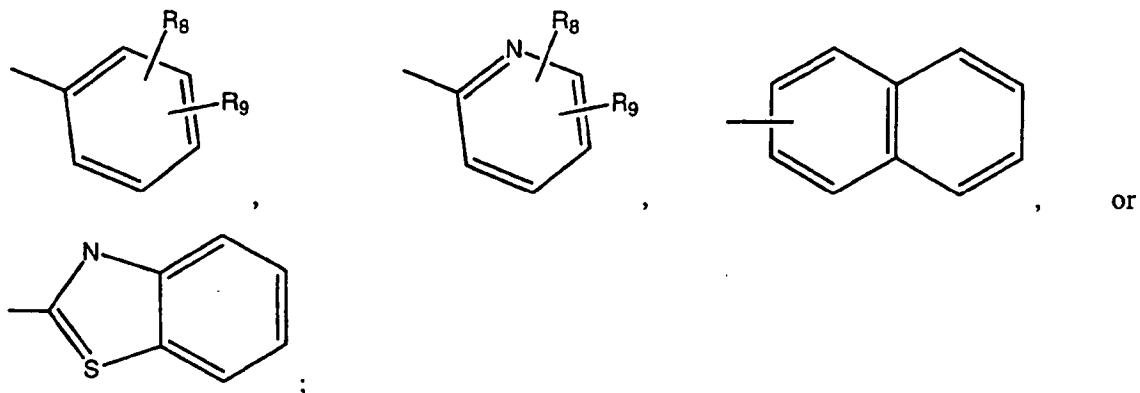
b) a moiety of the formulae:



wherein  $L^3$  is a chemical bond or a group selected from  $-CH_2-$ ,  $-CH_2-Z-$ ,  $-C(O)-$ ,  $-O-$ ,  $-S-$ , or  $-(CH_2)_n-Z-(CH_2)_n-$ ;

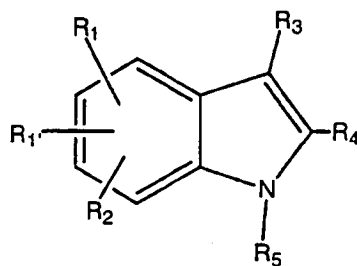
$M^3$  is selected from  $-(CH_2)_n-C_3-C_5$  cycloalkyl, furanyl, thienyl, pyrrolyl,





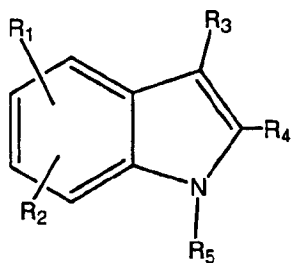
or a pharmaceutically acceptable salt thereof.

18. A compound of Claim 17 of the formula:



wherein  $R^{1'}$  and  $R^2$  are hydrogen, and the moieties  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^8$ ,  $R^9$  and  $R^{10}$ ,  $n$ ,  $L^1$ ,  $L^2$ ,  $M^1$  and  $M^2$  are as defined in Claim 17, or a pharmaceutically acceptable salt thereof.

19. A compound of the formula:

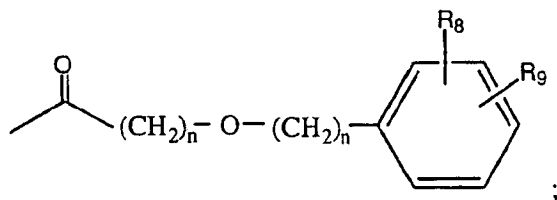


wherein

$R_1$  is selected from -O- $C_1$ - $C_6$  alkyl, -S- $C_1$ - $C_6$  alkyl, -O-phenyl, -S-phenyl, -O-benzyl, -S-benzyl, the alkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub>, or -OH;

$R_2$  is selected from H, halogen, -CF<sub>3</sub>, -OH, - $C_1$ - $C_{10}$  alkyl, preferably - $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy, -CHO, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH- $C_1$ - $C_6$  alkyl, -N( $C_1$ - $C_6$  alkyl)<sub>2</sub>, -N-SO<sub>2</sub>- $C_1$ - $C_6$  alkyl, or -SO<sub>2</sub>- $C_1$ - $C_6$  alkyl;

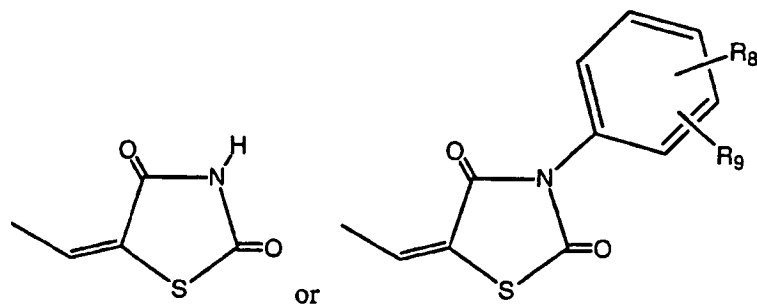
$R_3$  is selected from H, halogen, -CF<sub>3</sub>, -OH, - $C_1$ - $C_{10}$  alkyl, preferably - $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy, -CHO, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH- $C_1$ - $C_6$  alkyl, -N( $C_1$ - $C_6$  alkyl)<sub>2</sub>, -N-SO<sub>2</sub>- $C_1$ - $C_6$  alkyl, -SO<sub>2</sub>- $C_1$ - $C_6$  alkyl, or a moiety of the formula:



$n$  in each appearance is independently selected as an integer selected from 0-3;

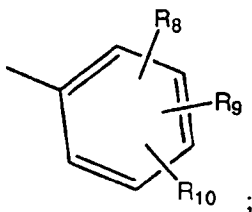
$R^8$  and  $R^9$  are independently selected in each appearance from H, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CF<sub>3</sub>, -OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, - $C_1$ - $C_6$  alkyl, -O- $C_1$ - $C_6$  alkyl, -NH( $C_1$ - $C_6$  alkyl), or -N( $C_1$ - $C_6$  alkyl)<sub>2</sub>;

$R_4$  is the moiety -L<sup>1</sup>-M<sup>1</sup> or

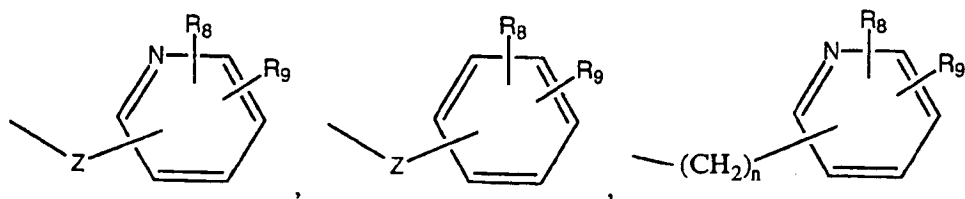


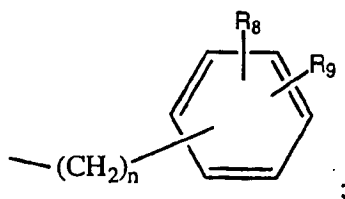
$L^1$  is selected from a chemical bond or a bridging group selected from  $-(CH_2)_n-O-$ ,  $-(CH_2)_n-S-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-C(O)-O-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

$M^1$  is the moiety:

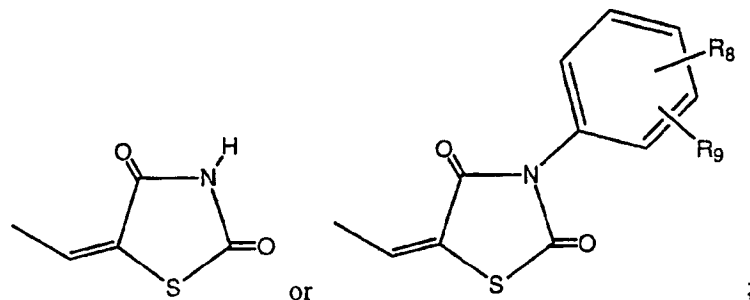


$R^{10}$  is selected from H,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-CF_3$ ,  $-OH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,





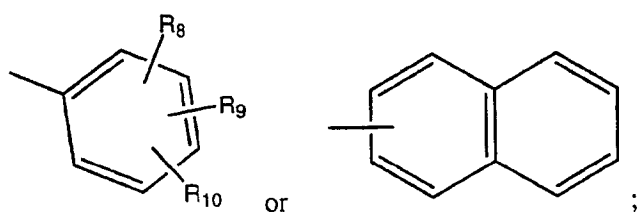
with a proviso that the combination of moieties comprising R<sup>4</sup> include a carboxylic acid or a moiety of the formulae:



R<sub>5</sub> is a structure of the formula  $-L^2-M^2$ ;

L<sup>2</sup> is selected from a chemical bond or a bridging group selected from  $-(CH_2)_n-O-$ ,  $-(CH_2)_n-S-$ ,  $-(CH_2)_n-O-(CH_2)_n-$ ,  $-(CH_2)_n-S-(CH_2)_n-$ ,  $-C(O)-O-$ ,  $-C(O)-(CH_2)_n-O-$ ,  $-C(O)-N-$ , or  $-(CH_2)_n-S-(CH_2)_n-C(O)-N-$ ;

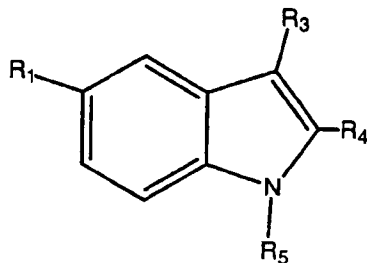
M<sup>2</sup> is selected from  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,



wherein R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined above;

or a pharmaceutically acceptable salt thereof.

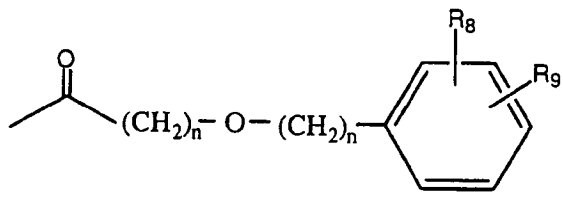
20. A compound of Claim 19 of the formula:



wherein

$R_1$  is selected from  $-O-C_1-C_6$  alkyl,  $-S-C_1-C_6$  alkyl,  $-O$ -phenyl,  $-O$ -benzyl,  $-S$ -benzyl, the alkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ , or  $-OH$ ;

$R_3$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl, preferably  $-C_1-C_{10}$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_{10}$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH-C_1-C_6$  alkyl,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-N-SO_2-C_1-C_6$  alkyl,  $-SO_2-C_1-C_6$  alkyl or a moiety of the formula:

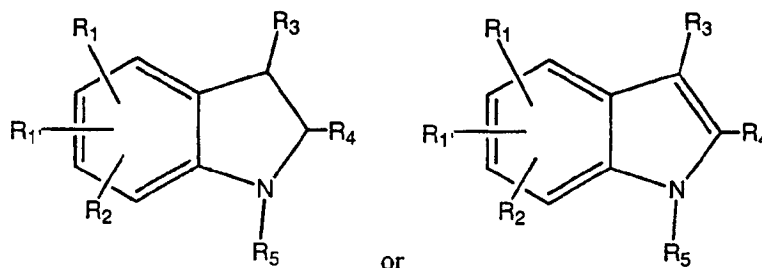


wherein  $R^4$ ,  $R^5$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  are as defined in Claim 19, or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

22. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 19, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

23. A compound of the formula:



wherein

$R_1$  and  $R_2$  are independently selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl, preferably  $-C_1-C_6$  alkyl,  $-S-C_1-C_{10}$  alkyl, preferably  $-S-C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ , phenyl,  $-O$ -phenyl,  $-S$ -phenyl, benzyl,  $-O$ -benzyl,  $-S$ -benzyl; or a ring moiety of the groups a), b) or c), below, directly bonded to the indole ring or bonded to the indole ring by a  $-S-$ ,  $-O-$  or  $-(CH_2)_n-$  bridge;

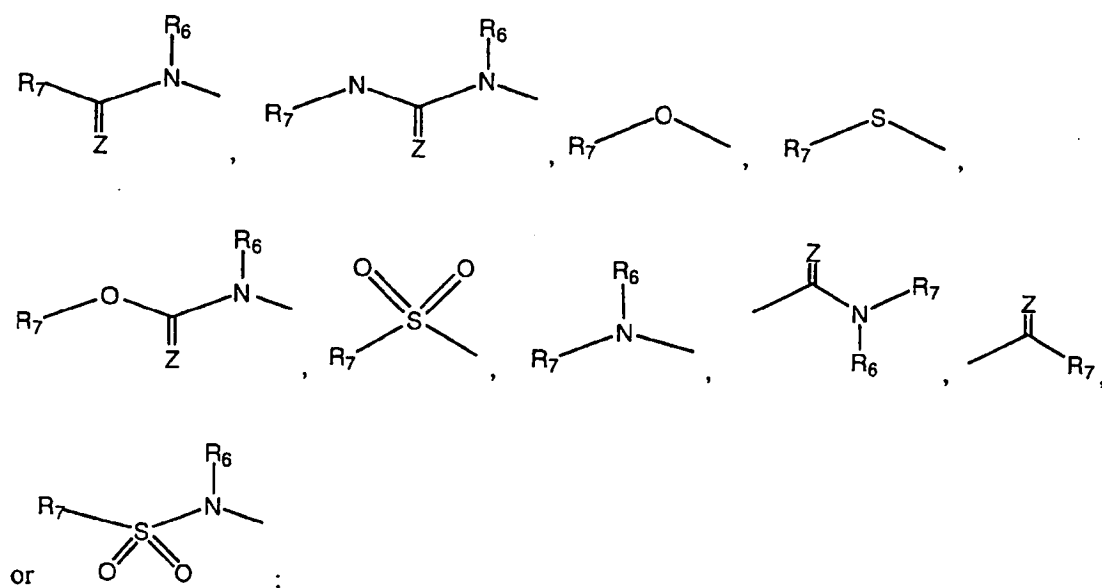
a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, oxathiazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ ; or

b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadiazine, oxazine, or morpholine, the six-

membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

c) a bicyclic ring moiety optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to benzofuran, chromene, indole, isoindole, indoline, isoindoline, naphthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine, quinazoline, cinnoline, phthalazine, or naphthyridine, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

d) a moiety of the formulae:



Z is O or S;

R<sub>6</sub> is selected from the relevant members of the group H, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-

benzyl, or -S-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub>, or -OH;

R<sub>7</sub> is selected from the relevant members of the group -OH, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub>, -NH-(C<sub>1</sub>-C<sub>6</sub> alkyl), -N-(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-N-(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, phenyl, -O-phenyl, benzyl, or -O-benzyl; or

a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, oxathiazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, or -CF<sub>3</sub>; or

b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadiazine, oxazine, or morpholine, the six-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

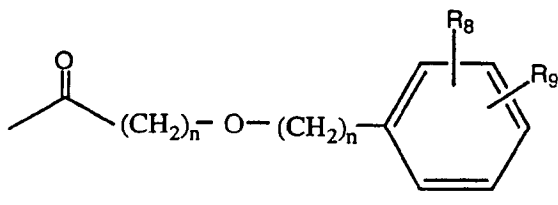
c) a bicyclic ring moiety containing from 8 to 10 ring atoms and optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to, benzofuran, chromene, indole, isoindole, indoline, isoindoline, naphthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine, quinazoline, cinnoline, phthalazine, or naphthyridine, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH;

n is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2;



$R_2$  is selected from H, halogen, -CN, -CHO, -CF<sub>3</sub>, -OH, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -N-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, or -SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl;

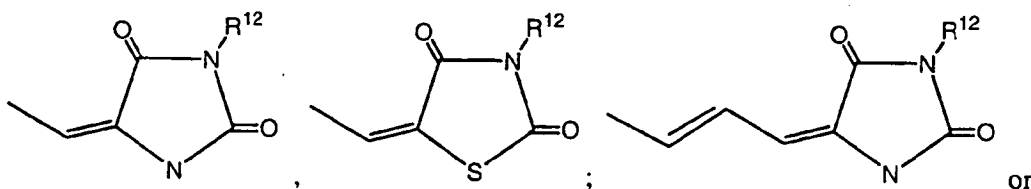
$R_3$  is selected from H, halogen, -CF<sub>3</sub>, -OH, -C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, -CHO, -C(O)CH<sub>3</sub>, -C(O)-(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -N-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, phenyloxy, benzyl, benzyloxy-C(O)-phenyl, -C(O)-benzyl, -CH<sub>2</sub>-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -C(O)-OH, C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)-O-C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)-CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-S-CH<sub>2</sub>-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), the rings of the relevant  $R_3$  groups being optionally substituted by from 1 to 3 groups selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NO<sub>2</sub>, -CF<sub>3</sub>, -C(O)-OH, or -OH; or a moiety of the formula:

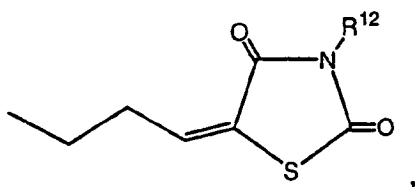


$n$  in each appearance is an integer independently selected from 0-3;

$R^8$  and  $R^9$  are independently selected in each appearance from H, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CF<sub>3</sub>, -OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -C<sub>1</sub>-C<sub>6</sub> alkyl, -O-C<sub>1</sub>-C<sub>6</sub> alkyl, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>;

$R_4$  is selected from -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CH=CH-COOH, tetrazole, -(CH<sub>2</sub>)<sub>n</sub>-tetrazole, the moiety -L<sup>1</sup>-M<sup>1</sup> or a moiety of the formulae:

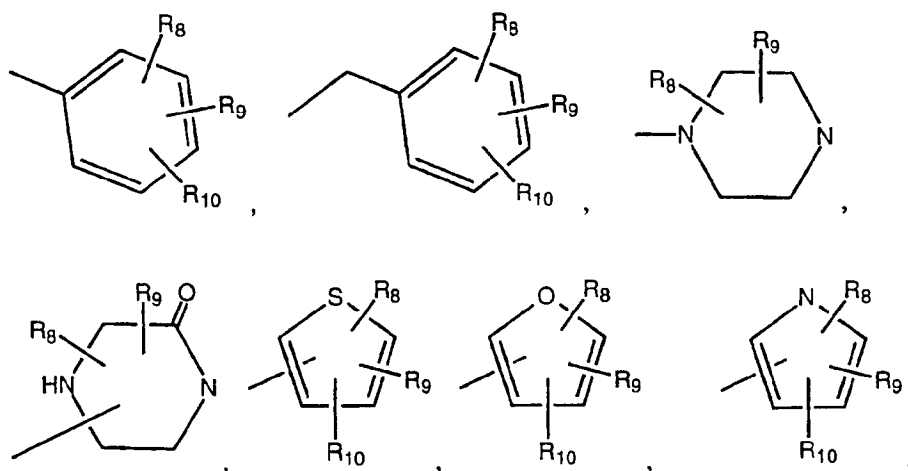


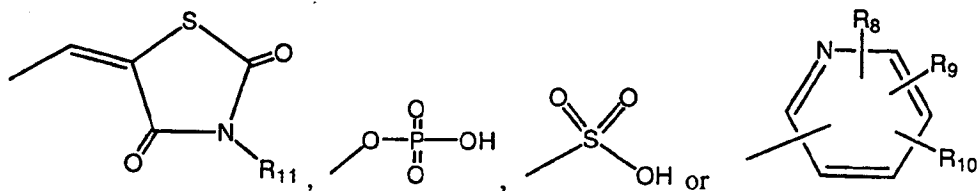
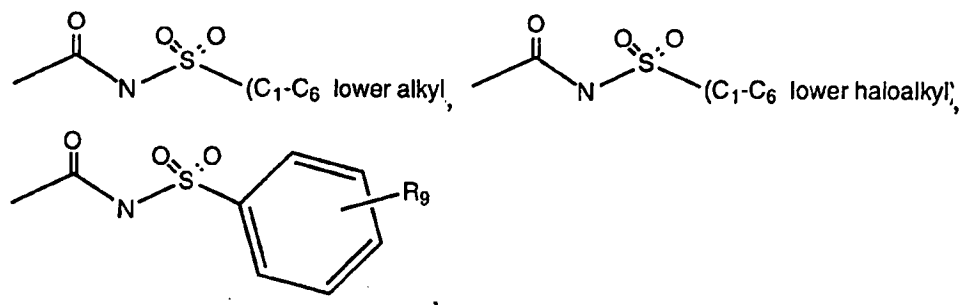


$R^{12}$  is selected from H,  $-CF_3$ ,  $C_1$ - $C_6$  alkyl,  $-(CH_2)_n$ - $C_3$ - $C_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-CF_3$ ,  $-OH$ ,  $-COOH$ ,  $-(CH_2)_n$ - $COOH$ ,  $-(CH_2)_n$ - $C(O)$ - $COOH$ ,  $-C_1$ - $C_6$  alkyl,  $-O$ - $C_1$ - $C_6$  alkyl,  $-NH$ ( $C_1$ - $C_6$  alkyl), or  $-N$ ( $C_1$ - $C_6$  alkyl) $_2$ ;

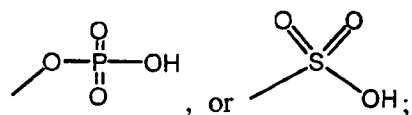
$L^1$  is selected from  $-(CH_2)_n$ -,  $-S$ -,  $-O$ -,  $-C(O)$ -,  $-C(O)-O$ -,  $-(CH_2)_n$ - $O$ -,  $-(CH_2)_n$ - $S$ -,  $-(CH_2)_n$ - $O$ -( $CH_2$ ) $_n$ -,  $-(CH_2)_n$ - $S$ -( $CH_2$ ) $_n$ -,  $-(CH_2)_n$ - $C(O)$ -( $CH_2$ ) $_n$ -,  $-(CH_2)_n$ - $O$ -( $CH_2$ ) $_n$ -,  $-(CH_2)_n$ - $S$ -( $CH_2$ ) $_n$ -,  $-C(Z)$ - $N(R_6)$ -,  $-C(Z)$ - $N(R_6)$ -( $CH_2$ ) $_n$ -,  $-C(O)$ - $C(Z)$ - $N(R_6)$ -,  $-C(O)$ - $C(Z)$ - $N(R_6)$ -( $CH_2$ ) $_n$ -,  $-C(Z)$ - $NH$ - $SO_2$ -,  $-C(Z)$ - $NH$ - $SO_2$ -( $CH_2$ ) $_n$ -,  $-C(O)$ -( $CH_2$ ) $_n$ - $O$ -,  $-C(O)$ - $N$ -, or  $-(CH_2)_n$ - $S$ -( $CH_2$ ) $_n$ - $C(O)$ - $N$ -;

$M^1$  is  $-COOH$  or a moiety selected from:



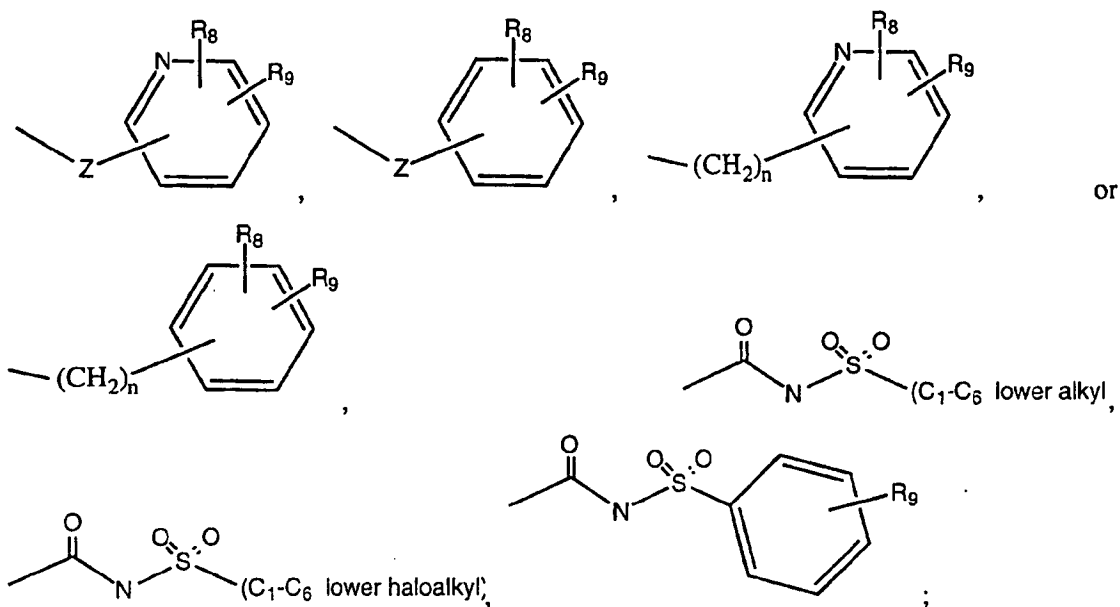


$\text{R}_8$ , in each appearance, is independently selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C(O)-COOH}$ , tetrazole,

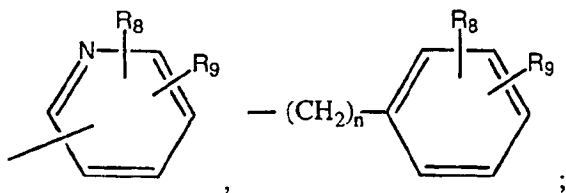


$\text{R}_9$  in each appearance is independently selected from H, halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C(O)-COOH}$ ,  $-\text{C}_1\text{-C}_6 \text{ alkyl}$ ,  $-\text{O-C}_1\text{-C}_6 \text{ alkyl}$ ,  $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ ;

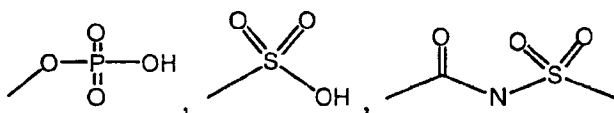
$\text{R}_{10}$  is selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C(O)-COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n\text{-C(O)-COOH}$ ,  $-\text{C}_1\text{-C}_6 \text{ alkyl}$ ,  $-\text{O-C}_1\text{-C}_6 \text{ alkyl}$ ,

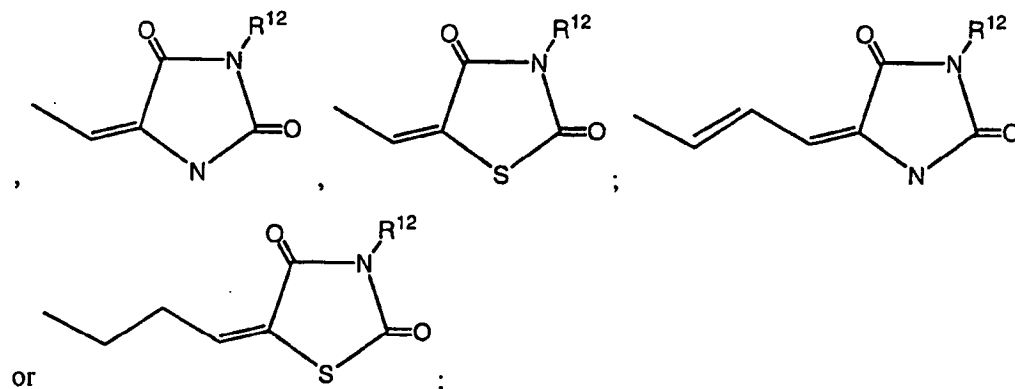


$R_{11}$  is selected from H,  $\text{C}_1\text{--C}_6$  lower alkyl,  $\text{C}_1\text{--C}_6$  cycloalkyl,  $\text{---CF}_3$ ,  $\text{---COOH}$ ,  $\text{---(CH}_2\text{)}_n\text{---COOH}$ ,  $\text{---(CH}_2\text{)}_n\text{---C(O)---COOH}$ ,



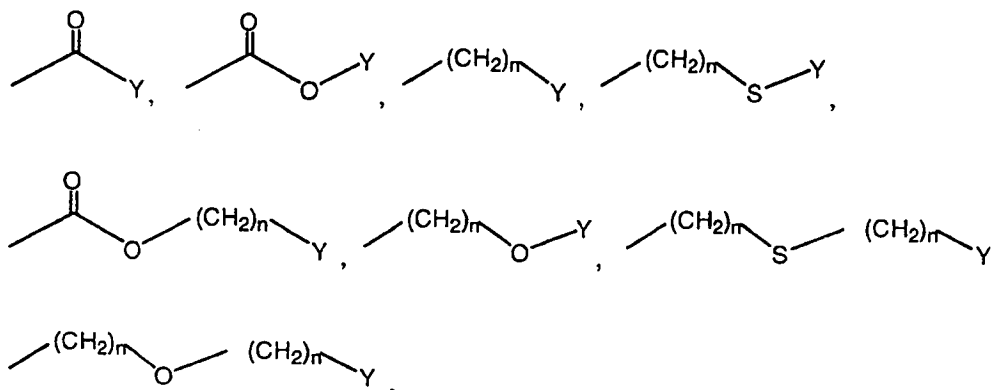
with a proviso that the moiety or combination of moieties comprising  $R_4$  include an acidic group selected from carboxylic acid, a tetrazole or a moiety of the formulae:





$R_5$  is selected from  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -S- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -O- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl, or the groups of:

a)  $-(CH_2)_n$ -phenyl-O-phenyl,  $-(CH_2)_n$ -phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -O-phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -phenyl-(O- $CH_2$ -phenyl) $_2$ ,  $-CH_2$ -phenyl-C(O)-benzothiazole or a moiety of the formulae:



wherein  $n$  is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2,

$Y$  is  $C_3$ - $C_5$  cycloalkyl or

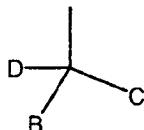
a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole,

isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, oxathiazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ , or  $-CF_3$ ; or

b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadiazine, oxazine, or morpholine, the six-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ; or

c) a bicyclic ring moiety containing from 8 to 10 ring atoms and optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to, benzofuran, chromene, indole, isoindole, indoline, isoindoline, naphthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine, quinazoline, cinnoline, phthalazine, or naphthyridine, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ;

d) a moiety of the formulae  $-(CH_2)_n-A$ ,  $-(CH_2)_n-S-A$ , or  $-(CH_2)_n-O-A$ , wherein A is the moiety:



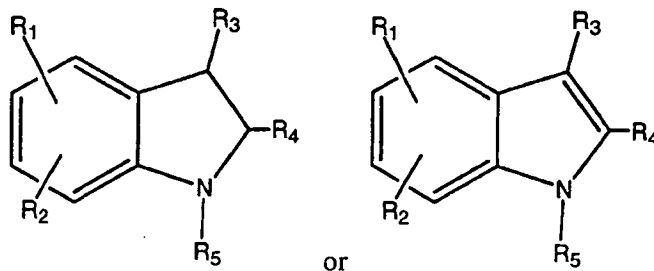
wherein

D is H,  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-CF_3$  or  $-(CH_2)_n-CF_3$ ;

B and C are independently selected from phenyl, pyridinyl, pyrimidinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen,  $-CN$ ,  $-CHO$ ,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-NH_2$  or  $-NO_2$ ;

or a pharmaceutically acceptable salt thereof.

24. A compound of Claim 23 having the formula:



wherein

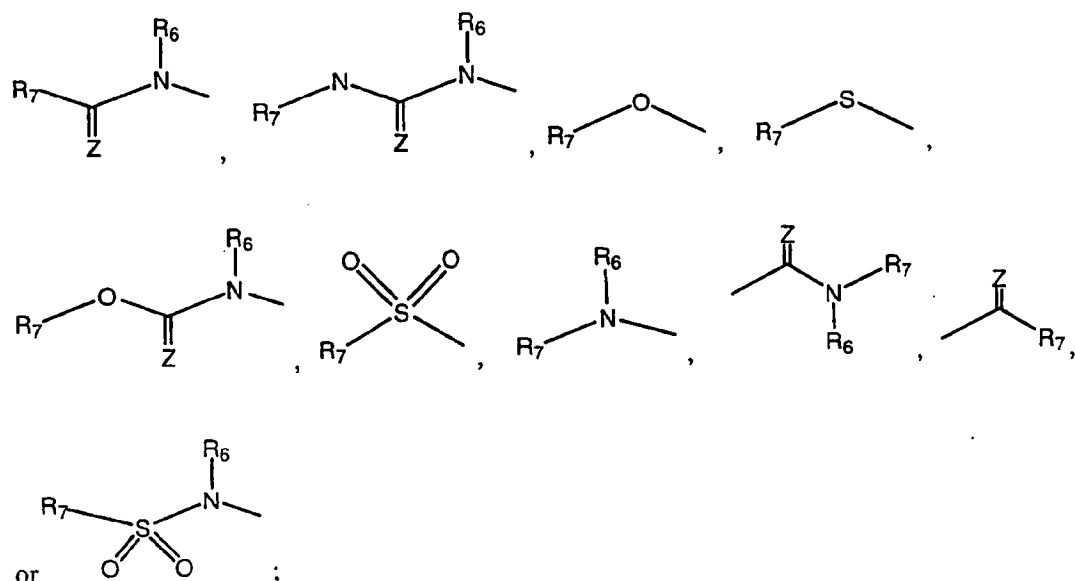
R<sub>1</sub> is selected from H, halogen, -CF<sub>3</sub>, -OH, -C<sub>1</sub>-C<sub>10</sub> alkyl, preferably -C<sub>1</sub>-C<sub>6</sub> alkyl, -S-C<sub>1</sub>-C<sub>10</sub> alkyl, preferably -S-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-benzyl, -S-benzyl; or a ring moiety of the groups a), b) or c), below, directly bonded to the indole ring or bonded to the indole ring by a -S-, -O- or -(CH<sub>2</sub>)<sub>n</sub>- bridge;

a) furan, pyrrole, or thiophene, being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub>; or

b) pyridine, pyrimidine, piperidine, or morpholine, each being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

c) benzofuran, indole, naphthalene, purine, or quinoline, each being optionally substituted by from 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -NO<sub>2</sub>, -NH<sub>2</sub>, -CN, -CF<sub>3</sub> or -OH; or

d) a moiety of the formulae:



Z is O or S;

$R_6$  is selected from the relevant members of the group H,  $-CF_3$ ,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-benzyl, or -S-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ , or  $-OH$ ;

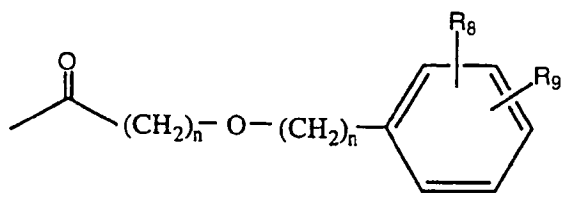
$R_7$  is selected from the relevant members of the group  $-OH$ ,  $-CF_3$ ,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-NH_2$ ,  $-(CH_2)_n-NH_2$ ,  $-NH-(C_1-C_6 \text{ alkyl})$ ,  $-N-(C_1-C_6 \text{ alkyl})_2$ ,  $-(CH_2)_n-NH-(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_n-N-(C_1-C_6 \text{ alkyl})_2$ , phenyl, -O-phenyl, benzyl, or -O-benzyl, furan, pyrrole, thiophene, pyridine, pyrimidine, thiazole, pyrazole, or morpholine the rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen,  $C_1-C_{10}$  alkyl, preferably  $C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CHO$ ,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$  or  $-OH$ ;



n is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2;

R<sub>2</sub> is selected from H, halogen, -CN, -CHO, -CF<sub>3</sub>, -OH, C<sub>1</sub>-C<sub>10</sub> alkyl, preferably C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, -CHO, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -N-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, or -SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl;

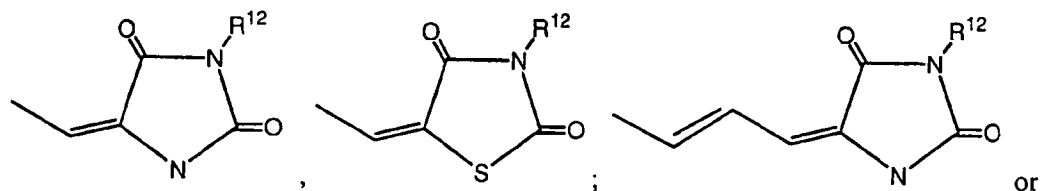
R<sub>3</sub> is selected from H, halogen, -CF<sub>3</sub>, -OH, -C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, -CHO, -C(O)CH<sub>3</sub>, -C(O)-(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -N-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, phenyloxy, benzyl, benzyloxy-C(O)-phenyl, -C(O)-benzyl, -CH<sub>2</sub>-(C<sub>3</sub>-C<sub>5</sub> cycloalkyl), -C(O)-OH, C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)-O-C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)-CF<sub>3</sub>, or -(CH<sub>2</sub>)<sub>n</sub>-S-CH<sub>2</sub>-(C<sub>3</sub>-C<sub>5</sub> cycloalkyl), the rings of the relevant R<sub>3</sub> groups being optionally substituted by from 1 to 3 groups selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NO<sub>2</sub>, -CF<sub>3</sub>, -C(O)-OH, or -OH; or a moiety of the formula:

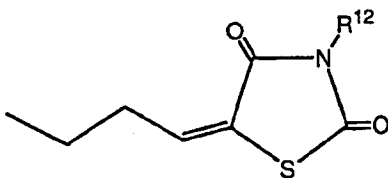


n in each appearance is independently selected as an integer selected from 0-3;

R<sup>8</sup> and R<sup>9</sup> are independently selected in each appearance from H, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CF<sub>3</sub>, -OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -C<sub>1</sub>-C<sub>6</sub> alkyl, -O-C<sub>1</sub>-C<sub>6</sub> alkyl, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>;

R<sub>4</sub> is selected from -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CH=CH-COOH, tetrazole, -(CH<sub>2</sub>)<sub>n</sub>-tetrazole, the moiety -L<sup>1</sup>-M<sup>1</sup> or a moiety of the formulae:

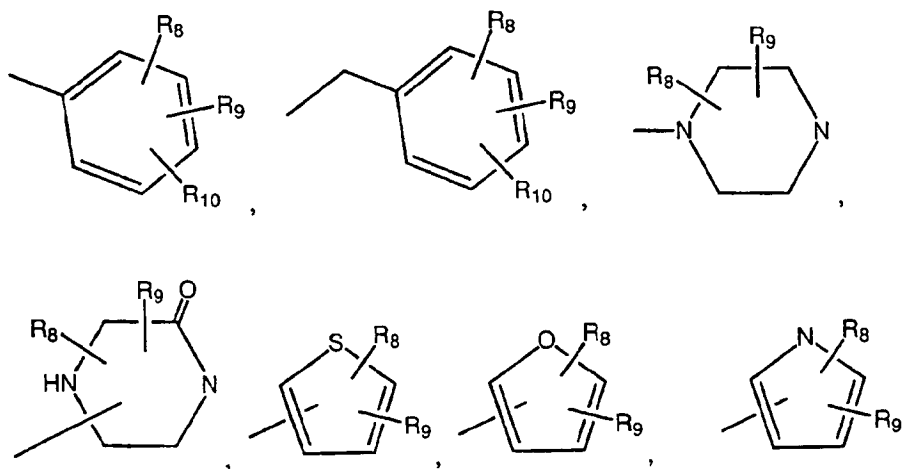


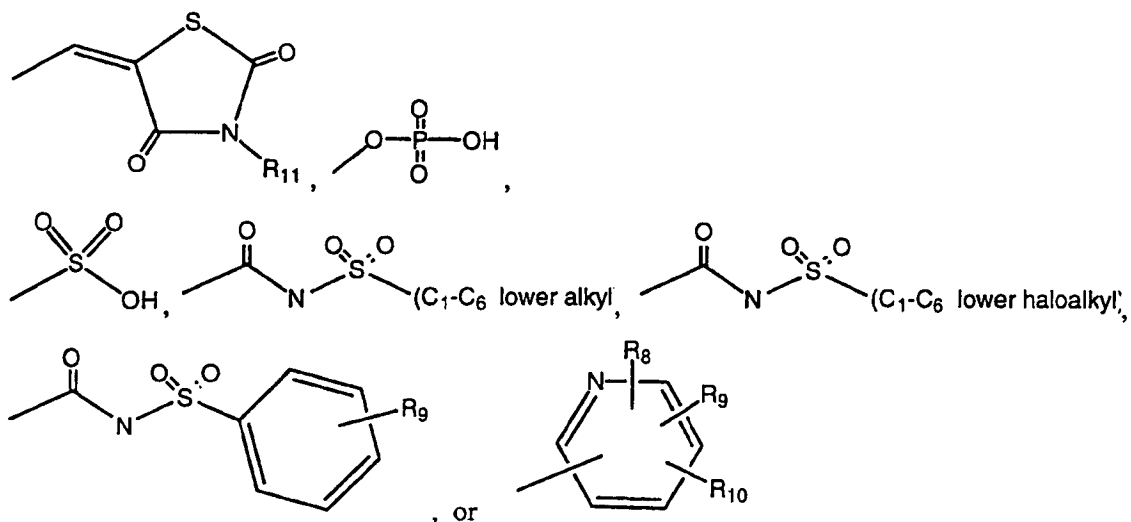


$R^{12}$  is selected from H,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $-(\text{CH}_2)_n\text{-C}_3\text{-C}_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C(O)-COOH}$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $-\text{O-C}_1\text{-C}_6$  alkyl,  $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ ;

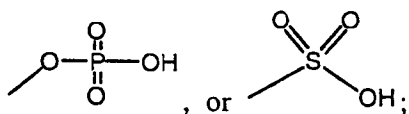
$L^1$  is selected from  $-(\text{CH}_2)_n-$ ,  $-\text{S}-$ ,  $-\text{O}-$ ,  $-\text{C(O)}-$ ,  $-\text{C(O)-O-}$ ,  $-(\text{CH}_2)_n\text{-O-}$ ,  $-(\text{CH}_2)_n\text{-S-}$ ,  $-(\text{CH}_2)_n\text{-O-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-C(O)-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-O-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n\text{-C(Z)-N(R}_6\text{)-}$ ,  $-\text{C(Z)-N(R}_6\text{)-(CH}_2)_n-$ ,  $-\text{C(O)-C(Z)-N(R}_6\text{)-}$ ,  $-\text{C(O)-C(Z)-N(R}_6\text{)-(CH}_2)_n-$ ,  $-\text{C(Z)-NH-SO}_2-$ ,  $-\text{C(Z)-NH-SO}_2\text{-(CH}_2)_n-$ ,  $-\text{C(O)-(CH}_2)_n\text{-O-}$ ,  $-\text{C(O)-N-}$ , or  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n\text{-C(O)-N-}$ ;

$M^1$  is  $-\text{COOH}$  or a moiety selected from:



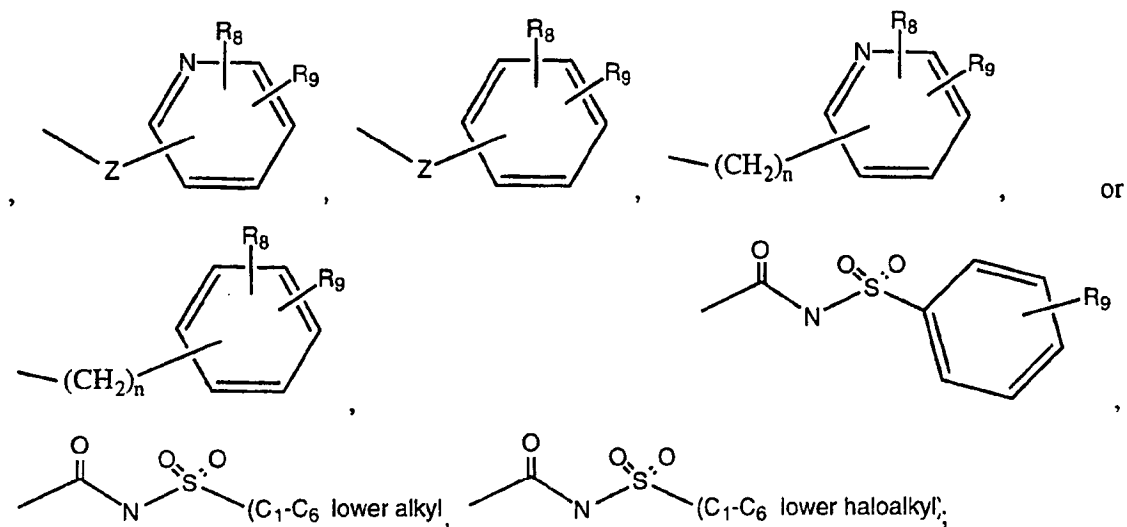


R<sub>8</sub>, in each appearance, is independently selected from H, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, tetrazole,

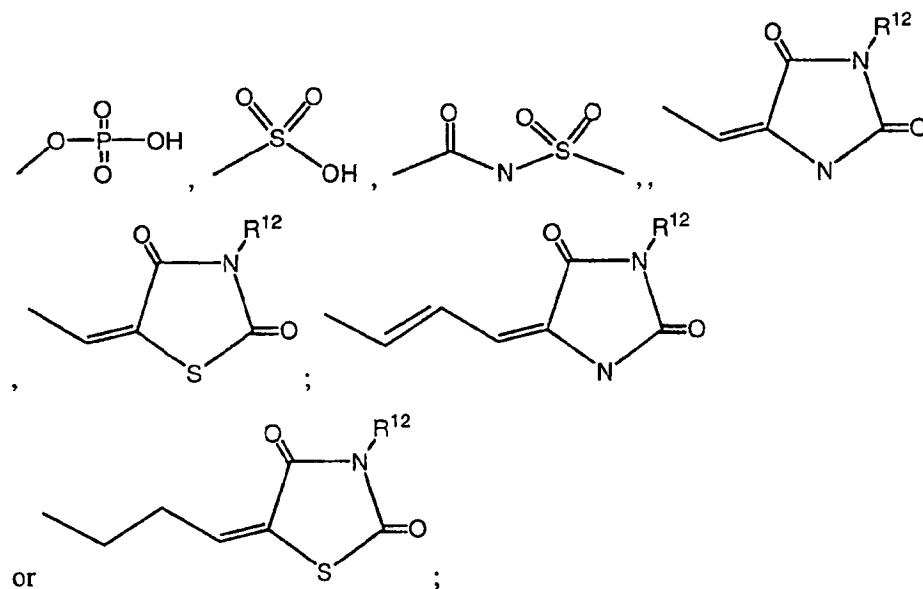


R<sub>9</sub> in each appearance is independently selected from H, halogen, -CF<sub>3</sub>, -OH, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -C<sub>1</sub>-C<sub>6</sub> alkyl, -O-C<sub>1</sub>-C<sub>6</sub> alkyl, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>;

R<sup>10</sup> is selected from H, -COOH, -(CH<sub>2</sub>)<sub>n</sub>-COOH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -CF<sub>3</sub>, -OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-COOH, -C<sub>1</sub>-C<sub>6</sub> alkyl, -O-C<sub>1</sub>-C<sub>6</sub> alkyl,

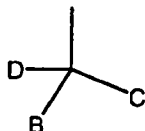


with a proviso that the moiety or combination of moieties comprising  $R_4$  include an acidic group selected from carboxylic acid, a tetrazole or a moiety of the formulae:



$R_5$  is selected from  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,

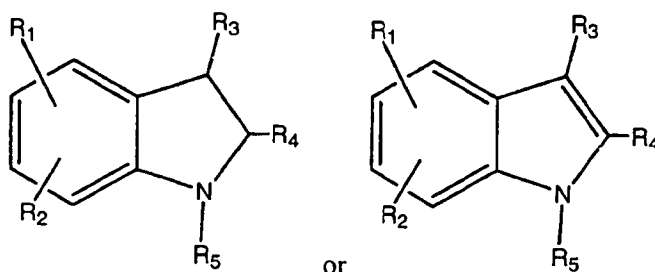
$-(CH_2)_n-S-(CH_2)_n-C_3-C_{10}$  cycloalkyl,  $-(CH_2)_n-O-(CH_2)_n-C_3-C_{10}$  cycloalkyl,  $-(CH_2)_n$ -phenyl-O-phenyl,  $-(CH_2)_n$ -phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -O-phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -phenyl-(O- $CH_2$ -phenyl)<sub>2</sub>,  $-CH_2$ -phenyl-C(O)-benzothiazole or a moiety of the formulae  $-(CH_2)_n-A$ ,  $-(CH_2)_n-S-A$ , or  $-(CH_2)_n-O-A$ , wherein A is the moiety:



D is H,  $C_1-C_6$  lower alkyl,  $C_1-C_6$  lower alkoxy,  $-CF_3$  or  $-(CH_2)_n-CF_3$ ;

B and C are independently selected from phenyl, pyridinyl, pyrimidinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen,  $-CN$ ,  $-CHO$ ,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy,  $-NH_2$  or  $-NO_2$ ; or a pharmaceutically acceptable salt thereof.

25. A compound of Claim 24 having the formula:



wherein

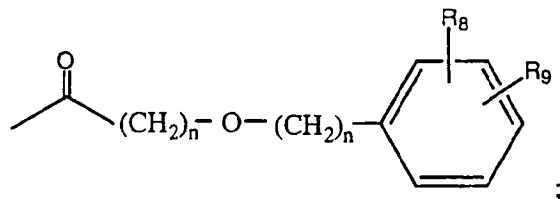
$R_1$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl, preferably  $-C_1-C_6$  alkyl,  $-S-C_1-C_{10}$  alkyl, preferably  $-S-C_1-C_6$  alkyl,  $C_1-C_{10}$  alkoxy, preferably  $C_1-C_6$  alkoxy,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ , phenyl,  $-O$ -phenyl,  $-S$ -phenyl, benzyl,  $-O$ -benzyl,  $-S$ -benzyl; or furan, pyrrole, or thiophene, bonded to the indole ring by a chemical bond or a  $-S-$ ,  $-O-$  or  $-(CH_2)_n-$  bridge, the phenyl, benzyl, furan, pyrrole, or thiophene rings being optionally substituted by from 1 to 3 substituents selected

from halogen,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-CF_3$ ; or

$n$  is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2;

$R_2$  is selected from H, halogen,  $-CN$ ,  $-CHO$ ,  $-CF_3$ ,  $-OH$ ,  $C_1$ - $C_{10}$  alkyl, preferably  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_{10}$  alkoxy, preferably  $C_1$ - $C_6$  alkoxy,  $-CHO$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH-C_1-C_6$  alkyl,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-N-SO_2-C_1-C_6$  alkyl, or  $-SO_2-C_1-C_6$  alkyl;

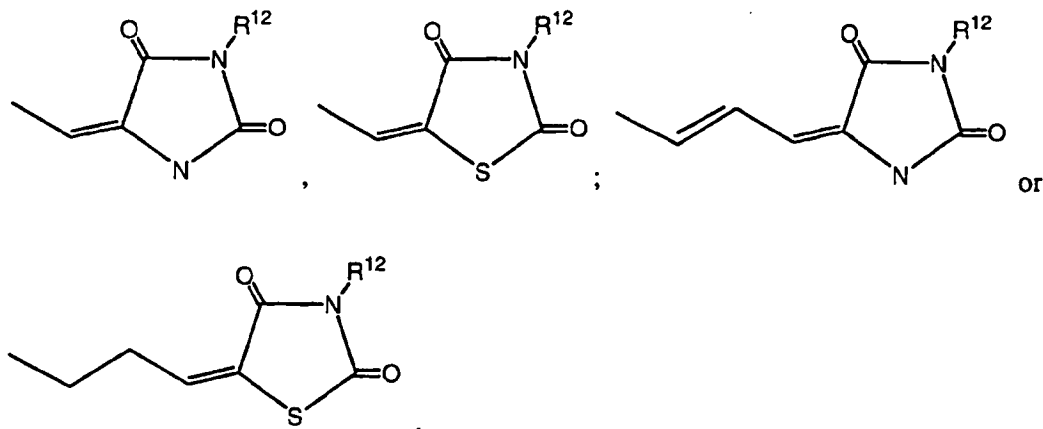
$R_3$  is selected from H, halogen,  $-CF_3$ ,  $-OH$ ,  $-C_1-C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy,  $-CHO$ ,  $-C(O)CH_3$ ,  $-C(O)-(CH_2)_n-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $-NH-C_1-C_6$  alkyl,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-N-SO_2-C_1-C_6$  alkyl,  $-SO_2-C_1-C_6$  alkyl, phenyl, phenyloxy, benzyl, benzyloxy- $C(O)$ -phenyl,  $-C(O)$ -benzyl,  $-CH_2-(C_3-C_5 \text{ cycloalkyl})$ ,  $-C(O)-OH$ ,  $C(O)-C_1-C_6$  alkyl,  $-C(O)-O-C_1-C_6$  alkyl,  $-C(O)-CF_3$ , or  $-(CH_2)_n-S-CH_2-(C_3-C_5 \text{ cycloalkyl})$ , the rings of the relevant  $R_3$  groups being optionally substituted by from 1 to 3 groups selected from halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-NO_2$ ,  $-CF_3$ ,  $-C(O)-OH$ , or  $-OH$ ; or a moiety of the formula:



$n$  in each appearance is independently selected as an integer selected from 0-3;

$R^8$  and  $R^9$  are independently selected in each appearance from H,  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-CF_3$ ,  $-OH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-C_1-C_6$  alkyl,  $-O-C_1-C_6$  alkyl,  $-NH(C_1-C_6 \text{ alkyl})$ , or  $-N(C_1-C_6 \text{ alkyl})_2$ ;

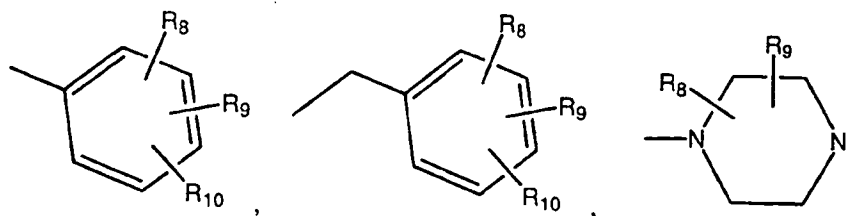
$R_4$  is selected from  $-COOH$ ,  $-(CH_2)_n-COOH$ ,  $-(CH_2)_n-C(O)-COOH$ ,  $-CH=CH-COOH$ , tetrazole,  $-(CH_2)_n$ -tetrazole, the moiety  $-L^1-M^1$  or a moiety of the formulae:

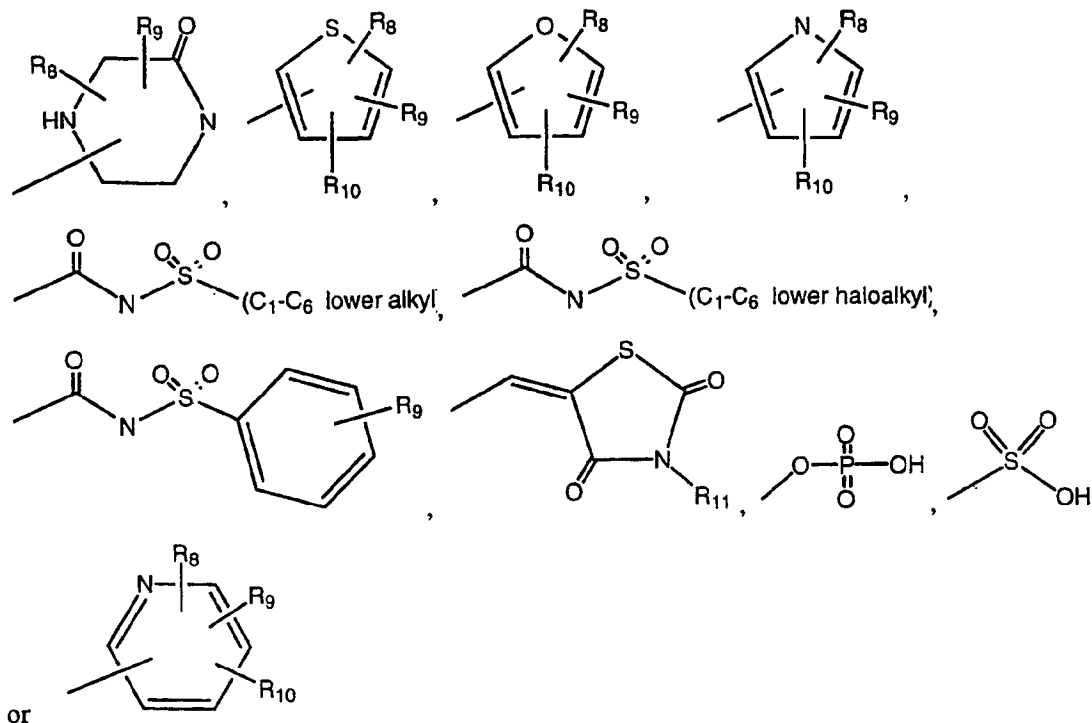


$R^{12}$  is selected from H,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $-(\text{CH}_2)_n\text{-C}_3\text{-C}_6$  cycloalkyl, phenyl, or benzyl, the cycloalkyl, phenyl or benzyl groups being optionally substituted by from 1 to 3 groups selected from halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n\text{-COOH}$ ,  $-(\text{CH}_2)_n\text{-C(O)-COOH}$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $-\text{O-C}_1\text{-C}_6$  alkyl,  $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ , or  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ ;

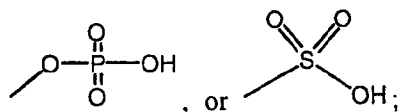
$L^1$  is selected from  $-(\text{CH}_2)_n-$ ,  $-\text{S}-$ ,  $-\text{O}-$ ,  $-\text{C(O)}-$ ,  $-\text{C(O)-O-}$ ,  $-(\text{CH}_2)_n\text{-O-}$ ,  $-(\text{CH}_2)_n\text{-S-}$ ,  $-(\text{CH}_2)_n\text{-O-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-C(O)-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-O-(CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n-$ ,  $-\text{C(Z)-N(R}_6)-$ ,  $-\text{C(Z)-N(R}_6)\text{-(CH}_2)_n-$ ,  $-\text{C(O)-C(Z)-N(R}_6)-$ ,  $-\text{C(O)-C(Z)-N(R}_6)\text{-(CH}_2)_n-$ ,  $-\text{C(Z)-NH-SO}_2-$ ,  $-\text{C(Z)-NH-SO}_2\text{-(CH}_2)_n-$ ,  $-\text{C(O)-(CH}_2)_n\text{-O-}$ ,  $-\text{C(O)-N-}$ , or  $-(\text{CH}_2)_n\text{-S-(CH}_2)_n\text{-C(O)-N-}$ ;

$M^1$  is  $-\text{COOH}$  or a moiety selected from:





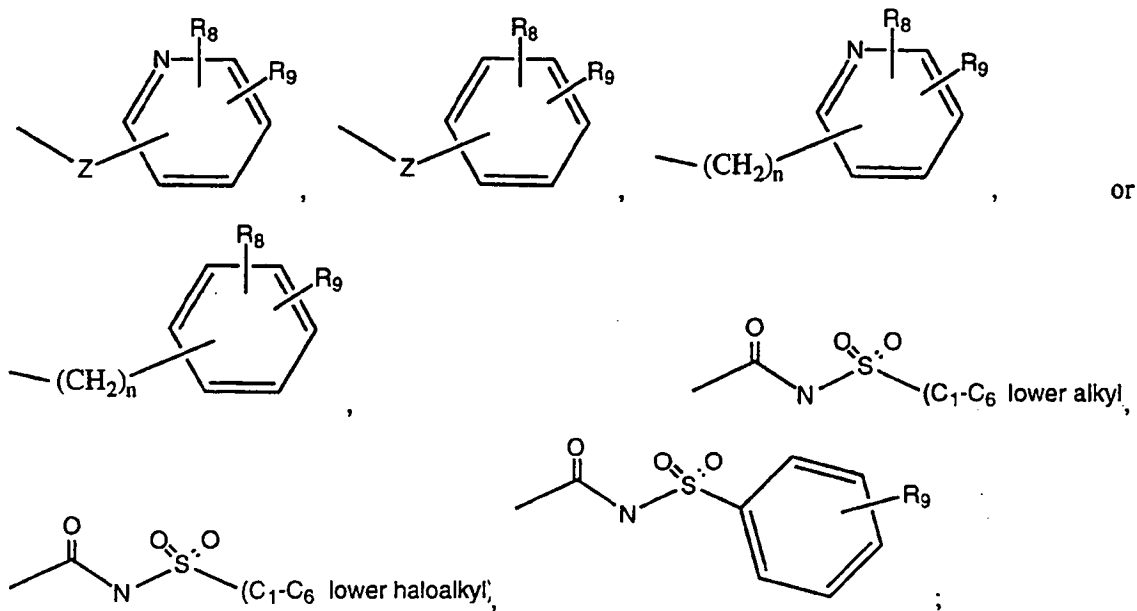
$\text{R}_8$ , in each appearance, is independently selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ , tetrazole,



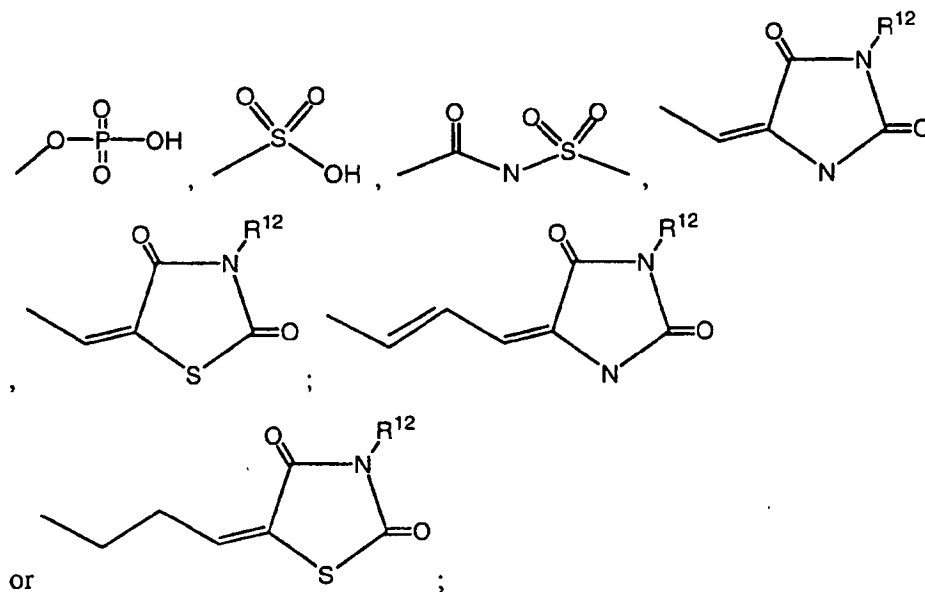
$\text{R}_9$  in each appearance is independently selected from H, halogen,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ ,  $-\text{C}_1\text{-C}_6$  alkyl,  $-\text{O}-\text{C}_1\text{-C}_6$  alkyl,  $-\text{NH}(\text{C}_1\text{-C}_6$  alkyl), or  $-\text{N}(\text{C}_1\text{-C}_6$  alkyl) $_2$ ;

$\text{R}_{10}$  is selected from H,  $-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{COOH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-(\text{CH}_2)_n-\text{C}(\text{O})-\text{COOH}$ ,  $-\text{C}_1\text{-C}_6$  alkyl,  $-\text{O}-\text{C}_1\text{-C}_6$  alkyl,

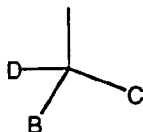




with a proviso that the moiety or combination of moieties comprising  $R_4$  include an acidic group selected from carboxylic acid, a tetrazole or a moiety of the formulae:



$R_5$  is selected from  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -S- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -O- $(CH_2)_n$ - $C_3$ - $C_{10}$  cycloalkyl,  $-(CH_2)_n$ -phenyl-O-phenyl,  $-(CH_2)_n$ -phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -O-phenyl- $CH_2$ -phenyl,  $-(CH_2)_n$ -phenyl-(O- $CH_2$ -phenyl)<sub>2</sub>,  $-CH_2$ -phenyl-C(O)-benzothiazole or a moiety of the formulae  $-(CH_2)_n$ -A,  $-(CH_2)_n$ -S-A, or  $-(CH_2)_n$ -O-A, wherein A is the moiety:



D is H,  $C_1$ - $C_6$  lower alkyl,  $C_1$ - $C_6$  lower alkoxy,  $-CF_3$  or  $-(CH_2)_n$ - $CF_3$ ;

B and C are independently selected from phenyl, pyridinyl, pyrimidinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen,  $-CN$ ,  $-CHO$ ,  $-CF_3$ ,  $-OH$ ,  $-C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-NH_2$  or  $-NO_2$ ; or a pharmaceutically acceptable salt thereof.

26. A compound of Claim 1 which is 4-[(5-{(E)-[5-(benzyloxy)-1-(4-{[3,5-bis(trifluoromethyl)phenoxy]methyl}benzyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)methyl]benzoic acid or a pharmaceutically acceptable salt thereof.

27. A compound of Claim 1 which is 5-[(E)-[5-(benzyloxy)-1-{3-[3,5-bis(trifluoromethyl)phenoxy]propyl}-1H-indol-2-yl]methylidene]-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.

28. A compound of Claim 1 which is 5-[(E)-[5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]methylidene]-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.

29. A compound of Claim 1 which is 5-{(E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene}-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.
30. A compound of Claim 1 which is 5-{(E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene}-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.
31. A compound of Claim 1 which is 5-{(E)-[1-(4-benzylbenzyl)-5-(benzyloxy)-1H-indol-2-yl]methylidene}-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.
32. A compound of Claim 1 which is 5-{(E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene}-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.
33. A compound of Claim 1 which is 5-{(E)-[5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]methylidene}-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.
34. A compound of Claim 1 which is 2-{5-{(E)-[5-(benzyloxy)-1-(4-{[3,5-bis(trifluoromethyl)phenoxy]methyl}benzyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)acetic acid or a pharmaceutically acceptable salt thereof.
35. A compound of Claim 1 which is 4-{5-{(E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)methyl}benzoic acid or a pharmaceutically acceptable salt thereof.
36. A compound of Claim 1 which is 2-{5-{(E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)acetic acid or a pharmaceutically acceptable salt thereof.
37. A compound of Claim 1 which is 4-{5-{(E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene}-2,4-dioxo-1,3-thiazolan-3-yl)methyl}benzoic acid or a pharmaceutically acceptable salt thereof.

38. A compound of Claim 1 which is 2-(5-((E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene)-2,4-dioxo-1,3-thiazolan-3-yl)acetic acid or a pharmaceutically acceptable salt thereof.

39. A compound of Claim 1 which is 5-((E)-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one or a pharmaceutically acceptable salt thereof.

40. A compound of Claim 1 which is 5-((E)-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one or a pharmaceutically acceptable salt thereof.

41. A compound of Claim 1 which is 5-((E)-{5-(benzyloxy)-1-[3-[3,5-bis(trifluoromethyl)phenoxy]propyl]-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one or a pharmaceutically acceptable salt thereof.

42. A compound of Claim 1 which is 5-((E)-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one or a pharmaceutically acceptable salt thereof.

43. A compound of Claim 1 which is 5-((E)-[1-(4-benzylbenzyl)-5-(benzyloxy)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one or a pharmaceutically acceptable salt thereof.

44. A compound of Claim 1 which is 5-((E)-[5-(benzyloxy)-1-(4-{{3,5-bis(trifluoromethyl)phenoxy}methyl}benzyl)-1H-indol-2-yl]methylidene)-2-thioxo-1,3-thiazolan-4-one or a pharmaceutically acceptable salt thereof.

45. A compound of Claim 1 which is 4-{{5-((E)-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]methylidene)-4-oxo-2-thioxo-1,3-thiazolan-3-yl}methyl}benzoic acid or a pharmaceutically acceptable salt thereof.

46. A compound of Claim 1 which is 5-((E)-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]methylidene)-2-thioxotetrahydro-4H-imidazol-4-one or a pharmaceutically acceptable salt thereof.

47. A compound of Claim 1 which is 1-benzyl-5-(2-thienyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

48. A compound of Claim 1 which is 5-(1-benzofuran-2-yl)-1-benzyl-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

49. A compound of Claim 1 which is 1-benzyl-5-(4-fluorophenyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

50. A compound of Claim 1 which is 1-benzyl-5-(3-methoxyphenyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

51. A compound of Claim 1 which is 1-benzyl-5-phenyl-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

52. A compound of Claim 1 which is 1-benzhydryl-5-bromo-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

53. A compound of Claim 1 which is 5-[3-(acetylamino)phenyl]-1-benzhydryl-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

54. A compound of Claim 1 which is 1-benzhydryl-5-(2-thienyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

55. A compound of Claim 1 which is 5-[(5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl)carbonylamino]-2-[(5-chloro-3-pyridinyl)oxy]benzoic acid or a pharmaceutically acceptable salt thereof.

56. A compound of Claim 1 which is 5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.
57. A compound of Claim 1 which is 5-(benzyloxy)-1-(4-{{3,5-bis(trifluoromethyl)phenoxy}methyl}benzyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.
58. A compound of Claim 1 which is 5-[(5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl}carbonyl)amino]-2-[(5-chloro-3-pyridinyl)oxy]benzoic acid or a pharmaceutically acceptable salt thereof.
59. A compound of Claim 1 which is 5-(benzyloxy)-1-(4-{{3,5-bis(trifluoromethyl)phenoxy}methyl}benzyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.
60. A compound of Claim 1 which is 4-{{5-((E)-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl}methylidene)-4-oxo-2-thioxo-1,3-thiazolan-3-yl}methyl}benzoic acid or a pharmaceutically acceptable salt thereof.
61. A compound of Claim 1 which is 5-((Z,2E)-3-{5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl}-2-propenylidene)-1,3-thiazolane-2,4-dione or a pharmaceutically acceptable salt thereof.
62. A compound of Claim 1 which is 5-(benzyloxy)-1-(4-{{3,5-bis(trifluoromethyl)phenoxy}methyl}benzyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.
63. A compound of Claim 1 which is 5-([1-benzyl-5-(benzyloxy)-1H-indol-2-yl]carbonyl)amino)isophthalic acid or a pharmaceutically acceptable salt thereof.

64. A compound of Claim 1 which is (E)-3-[5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]-2-propenoic acid or a pharmaceutically acceptable salt thereof.

65. A compound of Claim 1 which is (E)-3-[5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-1H-indol-2-yl]-2-propenoic acid or a pharmaceutically acceptable salt thereof.

66. A compound of Claim 1 which is (E)-3-[5-(benzyloxy)-1-(4-chlorobenzyl)-1H-indol-2-yl]-2-propenoic acid or a pharmaceutically acceptable salt thereof.

67. A compound of Claim 1 which is 1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indole-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

68. A compound of Claim 1 which is 5-([5-(benzyloxy)-1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indol-2-yl]carbonyl)amino)-2-[(5-chloro-3-pyridinyl)oxy]benzoic acid or a pharmaceutically acceptable salt thereof.

69. A compound of Claim 1 which is 3-([1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indol-2-yl]carbonyl)amino)benzoic acid or a pharmaceutically acceptable salt thereof.

70. A compound of Claim 1 which is 2-[4-([1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indol-2-yl]carbonyl)amino)phenyl]acetic acid or a pharmaceutically acceptable salt thereof.

71. A compound of Claim 1 which is 3-([3-acetyl-5-(benzyloxy)-1-(2-naphthylmethyl)-1H-indol-2-yl]methoxy)benzoic acid or a pharmaceutically acceptable salt thereof.

72. A compound of Claim 1 which is 4-{{[5-(benzyloxy)-1-(2-naphthylmethyl)-3-(2,2,2-trifluoroacetyl)-1H-indol-2-yl]methoxy}benzoic acid or a pharmaceutically acceptable salt thereof.

73. A compound of Claim 1 which is 3-{{[5-(benzyloxy)-1-[2,4-bis(trifluoromethyl)benzyl]-3-(2,2,2-trifluoroacetyl)-1H-indol-2-yl]methoxy}benzoic acid or a pharmaceutically acceptable salt thereof.

74. A compound of Claim 1 which is 2-({[3-acetyl-1-[4-(1,3-benzothiazol-2-ylcarbonyl)benzyl]-5-(benzyloxy)-1H-indol-2-yl]methyl}sulfanyl)acetic acid or a pharmaceutically acceptable salt thereof.

75. A compound of Claim 1 which is 2-({[3-acetyl-1-[4-(1,3-benzothiazol-2-ylcarbonyl)benzyl]-5-(benzyloxy)-1H-indol-2-yl]methyl}sulfanyl)benzoic acid or a pharmaceutically acceptable salt thereof.

76. A compound of Claim 1 which is 4-{{[3-acetyl-1-[4-(1,3-benzothiazol-2-ylcarbonyl)benzyl]-5-(benzyloxy)-1H-indol-2-yl]methoxy}benzoic acid or a pharmaceutically acceptable salt thereof.



# INTERNATIONAL SEARCH REPORT

Interr	ral A	mon No
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PCT, US 99/03388

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6	C07D417/06	A61K31/40	C07D409/04	C07D401/12	C07D403/04
	C07D209/22	C07D209/12	C07D209/10	C07D401/06	C07D209/42
	C07D209/14	C07D403/06	C07D405/04	C07D417/10	C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 13266 A (MERCKLE GMBH CHEM.-PHARM. FABRIK) 18 May 1995 see page 4; claim 19 ---	17,23
X	WO 98 05637 A (MERCKLE GMBH) 12 February 1998 * page 4 and 19 * ---	17,21,23
A	WO 97 05135 A (SHIONOGI & CO.,LTD.) 13 February 1997 see examples ---	17,19, 21,23
A	EP 0 620 215 A (ELI LILLY AND COMPANY) 19 October 1994 see claims ---	1,2
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

\*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

14 June 1999

Date of mailing of the international search report

28/06/1999

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# INTERNATIONAL SEARCH REPORT

Intern. Classification No.

PCT/US 99/03388

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 98 08818 A (GENETICS INSTITUTE, INC.)  5 March 1998  * complete document *</p> <p>-----</p>	1-13, 16

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 03388

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14-15  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 14-15  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: not applicable  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 03388

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims, i.e. the independent compound claims 1, 17, 19 and 23, the search was executed with due regard to the PCT Search Guidelines ( PCT/GL/2 ), C-III, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, i.e. phospholipase A2 inhibitors of formulas as illustrated by the working examples.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JS 99/03388

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9513266 A	18-05-1995	DE 4338770 A AU 7690794 A	18-05-1995 29-05-1995
WO 9805637 A	12-02-1998	AU 3767997 A NO 990413 A	25-02-1998 28-01-1999
WO 9705135 A	13-02-1997	AU 6530896 A CA 2227829 A CN 1197458 A EP 0848004 A	26-02-1997 13-02-1997 28-10-1998 17-06-1998
EP 620215 A	19-10-1994	AU 676884 B AU 5949294 A BR 9401482 A CA 2121323 A CN 1098715 A CZ 9400893 A FI 941767 A HU 70836 A JP 7025850 A NO 941361 A NZ 260298 A US 5684034 A ZA 9402615 A	27-03-1997 20-10-1994 18-10-1994 17-10-1994 15-02-1995 15-12-1994 17-10-1994 28-11-1995 27-01-1995 17-10-1994 28-05-1996 04-11-1997 16-10-1995
WO 9808818 A	05-03-1998	AU 4088297 A	19-03-1998

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